PATHOLOGY
of the HEART

Edited by

S. E. Gould, M.D., D.Sc.

Clinical Professor of Pathology, Wayne University College of Medicine
Detroit, Michigan

Pathologist, Wayne County General Hospital
Eloise, Michigan

Consultant in Pathology, Veterans Administration Hospital
Dearborn, Michigan

Editor, American Journal of Clinical Pathology



CHARLES C THOMAS · PUBLISHER

Springfield · Illinois · U.S.A.

CHARLES C THOMAS • PUBLISHER
Bannerstone House
301-327 East Lawrence Avenue, Springfield, Illinois, U S A

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD , OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

First Edition

Collaborators

Archie H Baggenstoss
Associate Professor of Pathologic Anatomy
Graduate School, University of Minnesota
Section on Pathologic Anatomy, Mayo Clinic
Rochester, Minnesota

Alexander Barry
Associate Professor of Anatomy
University of Michigan Medical School
Ann Arbor, Michigan

Jesse E Edwards
Assistant Professor of Pathologic Anatomy
Graduate School, University of Minnesota
Section on Pathologic Anatomy, Mayo Clinic
Rochester, Minnesota

Sylvester E Gould
Clinical Professor of Pathology
[illegible] College of Medicine
[illegible]
Pathologist, [illegible] Hospital
Eloise, Michigan

Harold D. Green
Professor of Physiology and Pharmacology
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Willard T. Hill
Associate Professor of Pathology
Northwestern University Medical School
Chicago, Illinois

Edward B Krumbhaar
Professor of Pathology (Emeritus)
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Alan R Moritz
Professor of Pathology
Western Reserve University School of Medicine
Cleveland, Ohio

Gordon B Myers
Professor of Medicine
Wayne University College of Medicine
Detroit, Michigan

Bradley M Patten
Professor of Anatomy
University of Michigan Medical School
Ann Arbor, Michigan

THE PATHOLOGY OF THE HEART

Otto Saphir
Clinical Professor of Pathology
University of Illinois College of Medicine
Pathologist, Michael Reese Hospital
Chicago, Illinois

Walter A. Stryker
Assistant Professor of Pathology
Wayne University College of Medicine
Detroit, Michigan
Pathologist, Wyandotte General Hospital
Wyandotte, Michigan

William B. Wartman
Professor of Pathology
Northwestern University Medical School
Chicago, Illinois

To My Wife

Foreword

MOST PATHOLOGISTS look on their subject as a large segment of the whole field of medicine, whereas some regard it as an independent science for the investigation of basic biological phenomena Naturally, these viewpoints are not mutually exclusive, a fact that is well exemplified in this volume. The practical aspects of the subject predominate, so that clinicians and pathologists will find a comprehensive survey of the information now available.

The book demonstrates beyond question that pathology in America has grown up, it has reached a stage of maturity which gratifies all its devotees Any scientific presentation is benefited by an appreciation of its historical background, especially when, as in this instance, the various aspects of pathological anatomy, disordered function, and clinical manifestations are well covered. The same approach is manifest in all the discussions, whether of embryology, normal anatomy, etiology, or any of the diseased states. Thus is integrated in each chapter that broad concept of cause, form, and function which modern pathology requires The material is carried over into the clinic by clear and adequate discussions of diagnosis and rational treatment. Moreover, the deficiencies of our present knowledge are so portrayed as to open many fields for future research

The editor is to be congratulated on his choice of contributors and the selection of subjects The authors of the various sections can be felicitated on the orderly, scientific, and thorough coverage of the fields in which they are unquestioned experts

This book is a superb contribution to the literature of pathology, medicine, and biology, and should be welcomed in the special field of cardiology It is to be anticipated that its reception will warrant repeated editions with opportunities for such revisions as the advances of science justify.

HOWARD T. KARSNER, M D.

Preface

UP TO THE PRESENT time there has been no adequate book embracing the pathology of the heart in the English language. In undertaking the preparation of such a volume the authors and the editor have attempted to present the essential factual data in a practical and understandable manner, not only for the pathologist but also for the clinician, and perhaps also for the medical student

A concise introductory chapter presents a restrained historical review of the subject in perspective. Next follow three chapters embodying the pertinent present knowledge of the embryology, the anatomy and the normal and pathologic physiology of the heart. The body of the treatise is devoted to the available authentic knowledge of cardiac pathology And finally, a chapter on clinicopathologic correlations supplements remarks on such correlations made within the content of the separate chapters on pathology The emphasis throughout on the clinical aspects of cardiac pathology is *deliberate since, in the last analysis, the lessons of pathology must be* brought into relation with the living patient

In order to avoid overlapping of discussion of the same topics by different authors it will be found that, although particular subjects may be mentioned at several points, in practically all such instances the subject has been given a relatively full discussion at one point only.

In preparation of this work, the editor has entertained the hope of realizing two objectives: first, that the data presented, so far as is possible, be accurate and authentic, and second, that all collaborators upon completion of their work regard their participation in this joint endeavor as having been worthy of the effort. The reader, however, must be the final judge of the worth of this volume In this connection the editor will welcome any advice, criticism or suggestion for improvement of this monograph, should the reception of this first edition warrant the publication of a second edition

It is a pleasure to acknowledge the splendid cooperation which the editor has received both from his collaborating authors and from the publisher.

Grateful acknowledgment is made to Dr. Carl V. Weller, Professor of Pathology, University of Michigan, for assistance rendered in planning the organization of this book, and to General Raymond O. Dart, former Director, and Dr Webb Haymaker of the Armed Forces Institute of Pathology for the use of illustrative material. Sincere appreciation is expressed to the many who in confidence have critically reviewed manuscripts of the several chapters, to Mrs. Roslyn K. Stempel, my former secretary, for conscientious review of manuscripts and preparation of copy, and to Miss Edith E Parris, Assistant Editor of the *American Journal of Clinical Pathology*, for advice and assistance in review of page proof. The editor also wishes to acknowledge his obligation to Dr. Roland M Athay, Superintendent of Wayne County General Hospital and Infirmary, and to

Wayne County Board of County Institutions, the governing body of the hospital, for their public-spirited support of this undertaking. And finally he wishes to offer a word of tribute in remembrance of Dr. Thomas K. Gruber, late Superintendent of this hospital, a wise and able administrator, and a true and beloved friend who gave encouragement to this task, as indeed he did to every worthy endeavor.

S. E. Gould

Contents

CHAPTER I

History of the Pathology of the Heart

EDWARD B. KRUMBHAAR

USEFUL KNOWLEDGE of the pathology of the heart—by "pathology" being meant all the changes produced by disease—is a relatively recent acquisition along the long path of medical history. The slowly accumulating knowledge of disordered cardiac structure and function produced little of practical value before the nineteenth century. Ancients even maintained that the heart was not subject to disease—*Cor non aegrotare posse*, as Hippocrates is said to have put it.* Galen's classification of types of heart disease (wounds and inflammations, pericarditis and pericardial effusions, palpitations) held the field for more than a thousand years. It was only in the fifteenth century that some of the grosser anatomic changes began to be observed. Pietro di Montagnano (died 1460), for instance, noted damaged hearts in 14 dissections at Padua.

Functional disturbances such as "palpitation" (frequently considered by Hippocrates) and arrhythmia (a term attributed to Galen) were naturally recognized much earlier, though interpretation of the former word at least was very different then from what it is now, and both were understood so vaguely that they contributed nothing of true value. In fact, an irregular pulse amounted to little more than an irregular pulse until instruments of precision * led to classification of the arrhythmias into recognizable types of greatly varying causation and significance (J. Mackenzie and Thomas Lewis). While consideration of these functional advances, which are of prime importance in the development of the recently established specialty of cardiology, may be left to the physiologist and clinician and to histories of the general subject, pathologists should remember and teach that they also are truly developments in the field of pathology, even if they were not chiefly contributed by professional pathologists. The same principles apply to other less obvious examples of cardiac pathologic physiology, such as palpitation in the modern sense, "irritable heart" (J. M. da Costa, 1867);

* This statement is offered by both Moon and Herrick as the basis for the notion that the heart cannot be diseased. The nearest that I, with the help of W. B. McDaniel II, have come to this notion is in Littré's translation of *de Morbis*: "Nullus in corde morbus subortur" (No disease *arises* in the heart), elsewhere *it is* stated that the heart does not labor with pain. It is suggested that "aegrotare" may be an early paraphrase of the original Greek, in which case Hippocrates should not be held responsible for the more glaring error.

* Waller's cardiac electrometer (1887), and Einthoven's electrocardiograph (1903).

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Tabula xxii. ad Observationem lxix. cor triplici ventriculo præditum ostendit.

A. *Cor triplici præditum ventriculo.*

B. B. *Duo dextri cordis ventriculi.*

C. *Sinister ventriculus.*

D. *Arteria pulmonaria ex utroque dextro ventriculo prodiens.*



Figure I-1. Kerckring's report (1670) of a heart with double right ventricle and pulmonary artery, showing the crudity of most 17th century illustrations *N B* The letters *BB* and *C* do not appear in the original illustration

cardiac pain (Heberden, 1768); cardiac murmurs, gallop rhythm (Bouillaud, 1847, Potain, 1887); cardiac dyspnea (Cheyne, 1818, Stokes, 1846); and cardiac edema.

Knowledge of the pathologic anatomy – *the basis for comprehension of almost* all pathologic phenomena – of the heart, grew slowly. Its development conveniently falls into three overlapping periods: the first, longest and least valuable, characterized by isolated observations of such material as chance offered, next, a 300-year period of systematized collections of clinicopathologic cases; and third, in the nineteenth and twentieth centuries, treatises and textbooks on the ever-increasing body of known facts and their underlying laws. Negligible through ancient, classical, and medieval times, the practical beginning of cardiac pathology may conveniently be located in the Renaissance with Benivieni's *De abditis causis morborum* (published posthumously, 1507). Of his 111 short chapters, one of the 20 with necropsy describes what seems to be an acute pericarditis (it is not clear whether by the cavity "cum pilis refertum" – stuffed with hairs – is meant that of the pericardium or of the cardiac chambers). Another case revealed a "polyp of the heart," a subject which remained in confusion well into the nineteenth century. However, the heart was long a minor contributor to the progress of the anatomic concept of disease Even in the great *Sepulchretum* (1679) of Bonetus, a systematic presentation of nearly 3000 clinicopathologic cases from the literature, we find few significant items of cardiac pathology, though there are dozens of cases of "palpitation" and a number of the so-called cardiac polyps, some even being thus diagnosed before death. Bauhin (1592), Tulp (1641), and Malpighi (*De polypo cordis,* 1686) were others who prolonged this fallacy, until Kerckring showed the dark red, easily removable kind of polyp to be merely a postmortem phenomenon (*Spicilegium anatomicum,* 1670, Obs 73). The error was only gradually eliminated as the gray, tightly adherent antemortem thrombus became differentiated from the loose red postmortem clot. Even in 1839, in the first edition of Gross' excellent *Elements,* polyps appeared as "polypous concretions," though in the third edition (1857) "polypous" was changed to "fibrinous." Kerckring also contributed to the pathology of congenital heart disease, his 69th observation showed an infant's heart with a double right ventricle (*cor triplici ventriculo*) and a pulmonary artery leading from each, to fuse later, as is well shown in his engraving (Figure I-1).

In the seventeenth century, with the increasing accumulation of single pathologic observations, the custom arose of publishing assembled cases, whether from the

literature or from personal observation, collections that at times reached large numbers. Thus, Bonetus in his *Sepulchretum* included 2934 observations (*i e.* cases) made by 470 authors, yet he reports very little about the heart One section, *De angina,* includes only five observations, and these are mostly not *pectoris.* These collections were conspicuously weak in their heart material, and even *Morgagni's great De Sedibus et Causis Morborum,* which is credited with generally establishing the anatomic concept of disease, contained much less about the heart than about other organs and systems However, we find reported the structural changes in a case of angina pectoris, one of the earliest accounts of heart block, cases of vegetative endocarditis — one associated with gonorrhea (other names, of course, being applied), a case of rupture of the heart, a case of congenital hypoplasia of the aorta. Morgagni had the great merit of correlating careful clinical study with autopsy findings, better than any of his predecessors and, for some years, of his successors as well One of the greatest medical figures of the eighteenth century, he (Figure I-2) also made a noteworthy contribution to knowledge of the pathology of the heart.


Figure I-2 Giovanni Battista Morgagni (1682-1771), by Angelica Kauffmann (From Castiglioni's *Storia di Medicina*)

Systematic descriptions of cardiac pathology, though not comparable to modern textbooks, had already begun to appear. An early example was Fernel's *Pathologia,* one of the chief divisions of his great *Universa Medicina* (1554) In it he grouped heart diseases under the peculiar headings of inflammation, erysipelas, *tumores contra naturam,* ulcer and wounds Vieussens' *Traité Nouveau de la Structure et des Causes du Mouvement du Coeur* (1715), on the other hand, was "the first to make serious contributions to our knowledge of diseases of the heart" (Moon) He dealt with true lesions (congenital anomalies, mitral stenosis and aortic regurgitation, pericardial inflammation, adhesions and effusions) and not with symptoms that were but vaguely comprehended He recognized that asthma and hydrothorax might be due to heart disease, and also had a good concept of the passive congestion resulting from valvular obstruction Lancisi (1728), who, according to Long, "laid the foundation for a true understanding of the heart," observed sclerotic and warty valves, and dwelt at some length on cardiac "aneurysms" (in the strict etymologic derivation of dilatation, a meaning that still applies to some varieties) Thus to him aneurysms were commoner in the atria than in the ventricles, and were least common in the left ventricle His handling of the etiology of heart disease was less successful, stressing congenital defects, long-continuing violent emotions or physical effort and palpitations. His contemporary, Albertini, fa..

heredity, and syphilis (using mercury in its treatment), as important causes of heart disease, and correlated dyspnea and pulmonary edema with cardiac disease (1726).

Senac's *De la Structure, de l'Action et des Maladies du Coeur* (1749), however, was the first extensive work devoted to the heart alone. The 11 chapters on Diseases of the Heart, contained much pathology. He recognized inflammations of all three layers, and that pericarditis might follow pneumonia or pleurisy or infectious fevers, that aneurysm (*i.e.*, dilatation) of the ventricle might be accompanied by hypertrophy. He considered tumors, abscesses, "ulcers" and wounds, as well as arrhythmia, palpitations and weak action (syncope).



Figure I-3. École de Médecine de Paris in the early 19th century, when French pathology was dominant (From a contemporary engraving in the Bibliothèque Nationale)

Textbooks of pathology, in the sense in which we use the term "textbook" today, may be said to have started modestly with Matthew Baillie's small *The Morbid Anatomy of Some of the Most Important Parts of the Human Body* (1793). The 24 pages of the chapters on The Heart and Pericardium touch briefly on inflammation, abscess, gangrene, polyp, aneurysm of the heart, fibrous, bony, and earthy thickening of the valves, rupture of valves and of myocardium, malformations and hypertrophy of the heart; and "white spot," inflammation, adhesions, dropsy, excessive dryness and "scrofulous tumors" of the pericardium. No case reports were included, except in the German translation. The early textbooks in France and Germany, such as Lobstein's *Traité d'Anatomie Pathologique* (1829, 1833) and Meckel's *Handbuch* (1812-18) dealt with general pathologic anatomy *only*, the *specialized pathology* often being covered by atlases. The first textbook of any size in this country, Samuel Gross' *Elements of Pathological Anatomy* (1839), on the other hand, was divided, as are most texts today, into General and Specialized Pathological Anatomy. In the latter portion, the heart and its membranes occupied only 40 of the 510 pages Rupture was regarded by Gross, and for a long time afterward, as "generally the result of ulceration or of the softening of fatty degeneration."

The French school, dominant in the early nineteenth century through Europe's political situation and French pioneer achievements in physical diagnosis, also set the pattern in the pathology of the heart, through two great clinicians, Corvi-



Figure I-4. René-Théophile-Hyacinthe Laennec (1781-1826). (From a miniature on ivory in the Faculty of Medicine of Paris)

sart and Laennec. Corvisart's *Essai sur les Maladies et les Lesions Organiques du Coeur* (1806), though clinical lectures with pathologic checks, established our present custom of considering heart disease according to its three layers (with a fourth class for diseases *contra naturam* and those affecting several tissues). He emphasized the frequency of organic heart disease – second only to pulmonary phthisis, correctly unraveled the tangled problem of polyps, distinguished between fatty infiltration and degeneration of the heart (the latter he said he had never seen), described rupture of chordae tendineae and papillary muscles, and included the conventionally accepted lesions as well as hydatids. Laennec (Figure I-4) in his *Traité de l'Auscultation Médiate* (1819 and 1826), largely followed Corvisart, however, with extensive correlation of his clinical and autopsy findings, he was able to attain greater precision in his descriptions. In his consideration of different sizes of the heart, he recognized that heart failure was seldom seen except in dilated hearts, with or without hypertrophy. He had learned that communications between the ventricles were not always congenital malformations. He was accurate in describing irregularities and murmurs, yet he made a false interpretation of the origin of the two normal heart sounds, and although he saw postmortem hemolytic staining of the valves he attributed it to inflammation.

Thereafter, the heart occupied increasing space in textbooks of pathology

To take up achievements in some of the special fields, we turn first to Congenital Malformations.

Congenital Heart Disease offers some good examples of a long random progress of pathologic knowledge in a given subject before integration. A number of its lesions had been observed and reported for centuries before the observations were coordinated and the knowledge adequately



Figure I-5 Carl Rokitansky (1804-1878) (From an original *carte de visite* photograph, College of Physicians of Philadelphia)

utilized Correlation began in the nineteenth century, as in Farre's *Malformations of the Human Heart* (1814) Peacock's work of the same name (1858) is the first comprehensive treatise that gathered much from the earlier and the prolific contemporary literature Yet comparison of his largely empirical explanations of the genesis of the congenital lesions with Rokitansky's (Figure I-5) *Die Defekte der Scheidewände des Herzens* (1875) shows the rapidity of progress in this field (Figure I-6) This can be ascribed to recently acquired embryologic knowledge, as well as to zeal in unearthing new kinds of malformations. This work also achieved the distinction, seldom reached in the biological sciences, of correctly predicting that certain unobserved cardiac anomalies would later be discovered. Among congenital anomalies Rokitansky's *Lehrbuch der pathologischen Anatomie* (third editi 1856) included acardia, ectopia,

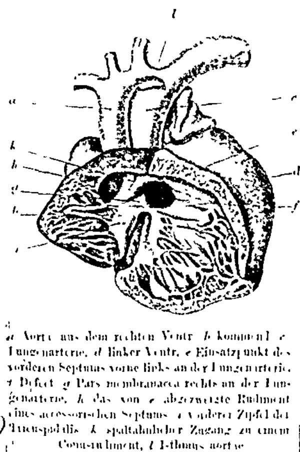


Figure I-6 Heart with transposed aorta and septal defect (From Rokitansky's *Die Defekte der Scheidewande des Herzens*)

chambered hearts, three chambers with either two atria or two ventricles, rudimentary ventricular septum with aorta arising from both ventricles, several varieties of defect of atrial and ventricular septa, patent ductus arteriosus, double heart, bifid apex, doubled great vessels, excessive (and insufficient) number of valve cusps, even the thebesian anomalies of position and size.* In fact Rokitansky mentioned so many varieties that his work has been criticized as having slavishly followed for each structure all the possibilities of general pathology. This process of assembling and reinterpreting has been carried on conspicuously in the present century by Maude Abbott (1869-1940, Figure I-7), whose whole professional life was devoted to the study of congenital heart disease.

Some of the early isolated findings proved to be premature, and some even retarded progress, as when Botallus (1565) and Gassendi (1630) used correct observations that openings might persist in the adult foramen ovale as arguments for the normal existence of a pervious cardiac septum. Harvey too had seen these persisting slits and also knew that various lower species had a common ventricle throughout life, but his marshalling of all the evidence and his logical deductions led him to the proper solution of this long-disputed problem. Vieussens is said by Corvisart (1806) to have noted premature occlusion of the foramen ovale in the fetus.

Ventricular septal defects are said to have been reported by observers as early as Stensen (1648-86), discoverer of the parotid duct. Simple defects were recognized by Corvisart as being sometimes



Figure I-7 Maude E. Abbott (1869-1940), a lifelong student of and contributor to the knowledge of congenital heart disease. (Courtesy of Armed Forces Institute of Pathology.)

* It was Laennec who suggested that a normal heart should be the size of the person's clenched fist.

congenital anomalies or at other times the result of inflammatory perforation. H. L Roger (1879) described the diagnosis of a simple ventricular defect by auscultation and recognized it as an anomaly (often harmless) rather than an organic disease (1879) Congenital cyanosis (*maladie bleu, morbus cæruleus*) goes back, as a clinical group at least, well into the eighteenth century. Senac is said by Abbott to have been the first to ascribe it to a defect of the ventricular septum Morgagni (1761) and William Hunter (1765) both observed the combination of stenosis of the pulmonary trunk with ventricular septal defect; and Sandifort (1777) described the train of symptoms that accompanies these lesions The septal defect, dextroposition of the aorta and pulmonary stenosis were well described and recognized as common by Farre in 1814 and by Peacock in 1858 Yet it was not until 1888 that the concise report of E L. A Fallot so established this as the commonest type of *morbus cæruleus* that it is now known to every medical student as the tetralogy of Fallot The "Eisenmenger complex," like the tetralogy, but without pulmonary stenosis, was first reported in 1897 (*Ztschr f. klin. Med.*). The rare "idiopathic dilatation of the pulmonary artery" we owe to B Zuber (1904) and B. S Oppenheimer (*Tr. A. Am. Physicians, 48* 290, 1933)

Of the heart as a whole, examples of double hearts had occasionally been observed (Zacutus Lusitanus, 1637), as well as bifid apices and lesser abnormalities of similar kind. Nonviable acardiac monsters and ectopia cordis are included in Andral's *Précis* (1829), as in several textbooks of the period. Baillie (1788) described true dextrocardia as part of a general transposition of viscera (*Phil. Trans. Roy. Soc London, 78*:350, 1788), and explained it as one of the three types of deviation from the normal creative action that produces structure, the others being deficiency and redundancy. A two-chambered heart is described in Farre's book, and Peacock cites two, though perhaps unreliable, from the seventeenth century (Pozzi, 1676, Lanzoni, 1691) His examples of three-chambered hearts start with Chemineau (1699) and continue with increasing frequency up to his time Such anomalies, amounting to different degrees of septal defects, reached their culmination in Rokitansky's magnificent *Die Defekte der Scheidewande des Herzens* (1875), classifying 11 varieties of ventricular and eight of atrial septal defects.

The several types of congenital transposition of the great vessels were well recognized by mid-nineteenth century Their pathogenesis, however, was but little understood. An aorta arising from both ventricles (*i.e.*, riding on a septal defect) appears in J R Farre's book (1814), he cites earlier descriptions by Sandifort and by William Hunter (1784) An early description of transposition is found in Baillie's text (1797), and many more had been reported by 1870 (especially in the *Transactions of the London Pathological Society*, and other English journals). To some, the anomaly seemed a spontaneous aberration, Peacock attributed it to faulty development of the aortic septum; Rokitansky, to a failure of the normal torsion of the aorta and pulmonary trunks. There the matter rested until Spitzer's (*Virchows Arch f. path Anat*, *243* 81-272, 1923) explanation, based on the reappearance of normally suppressed phylogenetic and ontogenetic phenomena, led to the detorsion theory (Figure I-8). In Maude Abbott's words (*Atlas*, p. 54):

". . . early arrest in the bulbar region of the primitive heart tube inevitably interferes with the clockwise torsion that takes place in this region in normal growth, any such lack of torsion (*i e.*, detorsion) will result in the obliteration of the normal human (left) aorta, and the persistence of

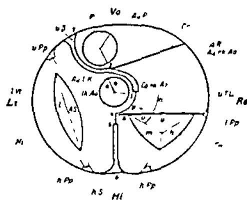


Abb 16 Normales Herz

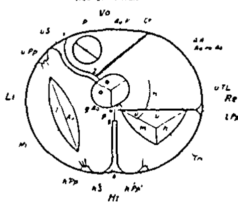


Abb 17 I Typus der Transposition reitende Aorta.

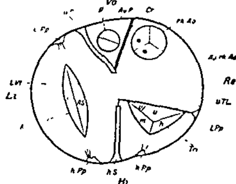


Abb 18 II Typus der Transposition einfache Transposition der Aorta

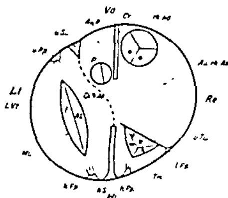


Abb 19 III Typus der Transposition gekreuzte Transposition beider arterieller Gefäße

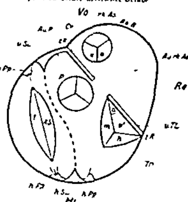


Abb. 20 IV Typus der Transposition gemischte Transposition beider arterieller Gefäße und des Ostium atrioventriculare dextrum

Figure I-8 Alexander Spitzer's diagrams of the four varieties of transposition of the great arteries of the heart, according to his detorsion theory

the reptilian right aorta, which is evanescent in the human embryo but now appears in permanent form as the 'transposed' vessel, standing in abnormal relation to the pulmonary artery and other right ventricular structures."

Together with this basic cause of transposition, concomitant changes in ridges (crista supraventricularis and tricuspid ridge), and the ventricular septum of several kinds are found, producing Spitzer's (1923) four types: (1, reitende; 2, simple; 3, crossed; 4, mixed) in place of the "true," "complete" and "corrected" transpositions of Rokitansky.

Size of Heart. Gross variations in the size of the heart, as might be expected, early attracted attention At one extreme, an adult heart weighing 3½ ounces (100 Gm) in a medium-sized woman of 40

without cardiac symptoms, was reported by Favelle (*Prov. M. and S J, London,* 5:358, 1843), whereas at the other extreme, Senac (*Book* 2) speaks of a heart weighing 15 lbs. (6 8 Kg) and cites others of 6 lbs. (Glaser), and the size of an infant's head (Baillou). Lancisi (1706) found cardiac weights of from 20 ounces to 3 pounds after emptying the cavities of blood; and T. H. Wright of Baltimore described one weighing 5 lbs, 3 oz. (2368 Gm) in a large Negro dying of heart failure (*Am J M. Sc., 12*.5, 1833). Vieussens, long before, had recognized that an enlarged heart was not compatible with perfect health. Hypertrophy of different chambers was not recognized until after the advent of a refined physical diagnosis (Corvisart, Laennec)

Lancisi appreciated that if the ventricles are dilated, the atria also will be, and that hypertrophy of the left ventricle might be accompanied by dilatation of the right side with signs of decompensation Two hundred years later, the French school distinguished between hypertrophy of each of the four chambers and also between dilatation of each. They recognized at the autopsy table concentric hypertrophy (where the cavity is diminished in size) the much commoner hypertrophy and dilatation (Corvisart's "active aneurysm"), and simple dilatation, a thin wall with little or no change in myocardial volume (Bertin, 1833). This last Corvisart, with etymologic correctness, called "passive aneurysm" The cardiac aneurysm of our modern parlance was called "partial dilatation" — tiresome distinctions these, but necessary to keep in mind if the earlier writings are to be properly comprehended.

Coronary Heart Disease. The story of what is today the most important of all cardiac disorders, coronary artery disease and its consequences, may be said to begin in 1768 with Heberden's (Figure I-9) vivid clinical description of angina pectoris and extends to our own times, when the distinction between coronary occlusion and angina pectoris without occlusion was first clearly established by J B. Herrick (1912) Incidentally, in Heberden's account, and he described many cases, the heart is mentioned but once, and then as being normal, and no indication has been found that he associated the pain with the heart Coronary "ossification" (today we read *calcification*), to be sure, had been correlated with angina-like pain several times in the past, by Morgagni (1761) among others Herrick says that Lancisi mentioned calcified coronaries as a cause of cardiac dilatation, and Senac associated them with true cardiac aneurysms (*i e.,* post-infarctional stretching) The great John Hunter, examining the heart of Fothergill's patient who had angina pectoris (1776), found that the two coronaries "were become as one piece of bone," but the connection between pain and lesion



Figure I-9 William Heberden (1710-1801), who first described angina pectoris (Contemporary engraving, after Sir William Beechey's portrait in the Royal College of Physicians)

was not considered When Hunter himself died (1793) in an anginal attack, his coronaries appeared as bony tubes, though not occluded (Major, p. 424). Herrick allots to Jenner and Parry (*Syncope Anginose*, 1799) the distinction of first attributing the chest pain to disease of the coronaries. Parry also glimpsed a causal relation between myocardial ischemia and the anginal attacks. Allen Burns (*Diseases of the Heart*, 1809) experimentally tied off the limb of an animal to test the theory of the ischemic origin of the pain, the same line was followed by Thomas Lewis only a few years ago, when he demonstrated that sharp pain was induced by exercising muscle deprived of its normal blood supply

Those who are puzzled as to why practical comprehension of coronary disease at the bedside should have had to await the discoveries of the twentieth century should read Herrick's description of the various events that account for this gap. a mixture of true observations that had to be rediscovered, errors typical of our halting medical progress, false theories that led seekers astray, wrongly evaluated experiments, *over-reliance on the long dominant method* of physical diagnosis, and the authoritative but erroneous views of Rokitansky and Virchow, together with a number of misleading designations for causes and effects (such as cardiac neurosis and fatty degeneration). In the field of etiology and pathogenesis, understanding of myocardial infarction and rupture necessarily had to wait for comprehension of the concepts of thrombosis and embolism (Virchow, 1846) and necrosis (Weigert, 1880). In fact, understanding of the role of coronary stenosis without occlusion and of spasm in coronary disease still lags, though it is still being actively pursued by clinicopathologic and experimental methods.



Figure I-10 Karl Albert Ludwig Aschoff (1866-1942) (Photograph taken in the autopsy room of the Philadelphia General Hospital, 1926)

Cardiac Rupture. Rupture of the myocardium has been known for at least 300 years, Harvey having found at autopsy a *tear in the left ventricle, presumably in* an infarcted area (1647). Morgagni reported several similar accidents and is said to have died of one himself. Its predisposing cause, however, was generally thought, until some 25 years ago, to be a fatty degeneration of the heart muscle, an error to be ascribed to the pre-microscopic authority of Richard Quain (1850) and continued, notwithstanding Elleaume's (Paris thesis, 1857) insistence on the dominating role of the coronary lesions and Weigert's clear exposition of the necrotic nature of the softened muscle (1880). *The ancients' belief that injuries* of the heart were necessarily fatal persisted to the end of the nineteenth century, in spite of numerous reports in the literature

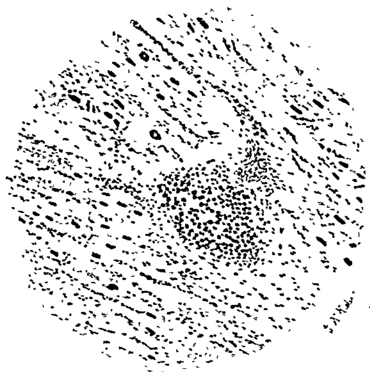


Figure I-11 An early illustration of an Aschoff body (From the second edition of Aschoff's *Lehrbuch der pathologischen Anatomie*)

to the contrary Gould and Pyle (1937) devoted several pages to this subject

Rheumatic Heart Disease. A connection between acute articular rheumatism (rheumatic fever) and heart disease was not even suspected until the end of the eighteenth century In this connection what was for more than a century the most important of heart diseases seems to have first appeared in print in the second edition of Baillie's *Morbid Anatomy* (1797) This idea he got from his patient, Dr. David Pitcairn, who had mentioned it in his clinical lectures (1788) Jenner also reported, to the Fleece Medical Society on a "Disease of the Heart following Acute Rheumatism," but this was not published, and his manuscript was never found. This correlation was accepted by British physicians (W. C. Wells, 1812, Hawkins's Gulstonian lectures, 1826), but such was the predominance of French medicine at that time that Bouillaud is usually credited for establishing this relationship as regards "the fibrous tissue of the heart" (1835) A myocardial connection, as might be expected, came gradually and considerably later Myocardial "induration" was an ancient concept which obviously included fibrosis due to various causes as well as to acute rheumatic fever It was not until Ludwig Aschoff (Figure I-10) in 1904 described, in addition to diffuse interstitial changes, the characteristic nodule (Figures I-11 and I-12) which bears his name that this most important of the three heart layers definitely entered the rheumatic picture. Without the aid of the Aschoff nodule, diagnosis of diffuse myocarditis of rheumatic origin is still uncertain, and "nonspecific" myocarditis still appears in textbooks to cover various conditions of

dabei eigentümliche
Knötchen zu finden, welche für die rheumatische Myocarditis spezifisch zu
sein schie[illegible]
nerender [illegible]
nach gena [illegible]
Sie lagen [illegible]
fäße, zeigt [illegible]
es bestand gleichzeitig eine Erkrankung aller Gefäßwandschichten, wie
sie für die Arteriitis nodosa beschrieben worden ist. Die erwähnten

Knötchen sind außerordentlich klein, höchstens submiliar, und entstehen durch Zusammenlagerung auffallend großer Elemente mit einem oder mehreren abnorm großen, leicht eingekerbten oder polymorphen Kernen. Die Zusammenlagerung der Zellen erfolgt oft in Form eines Fächers oder einer Rosette. Die Peripherie wird von den großen Kernen, das Zentrum von dem oft zu einer schwächeren oder anders färbbaren anscheinend nekrotischen Masse zusammenfließenden Protoplasma der Zellen gebildet. Bei flüchtiger Betrachtung erinnern die fächerförmigen Herde an kleinste Gichtnekrosen mit peripherem Zellmantel, wie man sie häufig in Gichtnieren findet. In den rheumatischen Knötchen handelt es sich aber nicht um tuberkulöse oder Fremdkörperriesenzellen mit mehreren regelmäßig geformten Kernen, sondern um Gebilde, die mehr an die großkernigen Elemente in gewissen Sarkomen oder in pseudoleukämischen Wucherungen erinnern. Allerdings bestehen die Knötchen
nicht ausschließlich aus solc[illegible]
große Lymphocyten, auch [illegible]
wenigstens in der Periphere [illegible]
eine periphere Zone, von der [illegible]
Bindegewebssepten erstreck[illegible]
sich noch vereinzelte großke[illegible]
fachen größeren leukocytoid[illegible]
in der Umgebung der kleinsten Gefäße finden und bei allen Entzündungen sehr deutlich hervortreten. Diese leukocytoiden Elemente sind die großen Zellen, die schon Hayem und Romberg beschrieben haben, deren Genese ihnen aber unklar blieb. Aus diesen großen Zellen, den entzündlich geschwollenen Adventitiazellen der Gefäße entstehen die riesenzellenähnlichen großkernigen Elemente, welche, vereinzelt oder zu Knötchen zusammengelagert, den rheumatischen Zellwucherungen ein eigentümliches Gepräge verleihen. Noch sei bemerkt, daß die Zahl eosinophil gekörnter Zellen in diesen Knötchen eine sehr geringe ist.

Während in dem einen Falle die Knötchenbildung den Eindruck einer frischen Zellwucherung machte, ließ sich in dem anderen Falle eine partielle oder totale fibröse Umwandlung der Knötchen nachweisen.

Figure I-12. Text of Aschoff's original description of the specific "Knötchen" (Excerpt from his communication in *Verhandl d deutsch path. Gesellsch*, 8 51, 1904.)

well- or ill-defined etiology—usually the latter. It is noteworthy, too, that for this, the most significant of all infectious diseases of the heart, the problem of its etiology and pathogenesis still remains unsolved.

Cardiac Syphilis. Syphilis, which until recent years constituted the third of a great triad of cardiac disorders, is now rapidly receding to a position of minor importance. Knowledge of cardiac syphilis was acquired more slowly than in the case of syphilis of other viscera. Proksch (*Die Geschichte der venerischen Krankheiten*, *Bonn*, 1895) and Lewis Connor (*J.A.M.A.*, *102*:575, 1934) attribute much of this delay to the authoritative John Hunter's conception of gonorrhea and syphilis as one disease. Syphilitic lesions of the heart were identifiable only with much difficulty before the discovery of *Treponema pallidum* and the acquisition of intimate knowledge of the microscopic changes characteristic of the disease. Syphilitic pericarditis and mural endocarditis are now regarded as practically nonexistent, except rarely by extension from the adjacent myocardium and root of the aorta. Narrowing of the coronary ostia, by syphilitic aortitis, with

production of coronary insufficiency, was first described by Jakob (*Erlangen Dissertation*, 1891). Cardiac lesions in syphilitics, to be sure, had been recorded from the times of Paré and Lancisi, but with no indication as to whether the lesions themselves were syphilitic In the myocardium, one of the oldest authenticated examples of syphilis is a gumma of the septum of a heart deposited in the Pennsylvania Hospital Museum in 1879 This was examined in 1907 by G C. Robinson (*Bull. Ayer Clin Lab., No. 4*, 1908), who, by correlating it with the patient's history and the record of a pulse rate of some 30 beats per minute and occasionally still lower, established the earliest known example of heart block due to gumma. That syphilis could cause both gummatous and diffuse interstitial changes in the myocardium was established by Virchow (1858). Both varieties have been thought to be rare by almost everyone but Warthin (1914), who believed that the diffuse variety was common even in adults, that it had a specific microscopic picture and that not infrequently treponemata could be demonstrated.

Pericardium. Senac, who devoted 30 pages to diseases of the pericardium, was familiar with the shaggy acute and indurated chronic inflammations, some of the latter apparently tuberculous, others of rheumatic origin. He was not the earliest to be acquainted with pericardial hydrops which sometimes produced "a monstrous dilatation," and he recognized that the sac might also contain blood, air or pus He cited two pericardial "tumors" found by Galen (a cystic tumor in a monkey and a scirrhus in a rooster), but we may well be skeptical as to their neoplastic nature, as was Senac himself of Galen's conjecture that they might occur in man Tumors and cysts had also been reported by Bonetus Senac regarded abscesses and ulcers of the pericardium, some undoubtedly tuberculous, as common. Senac recounts descriptions by Lower, Vieussens, Lancisi, Haller and others of adhesions, often apparently complete, of the two pericardial layers, and adds two cases of his own, one in which "the two ventricles were adherent in three or four places" and a second in which the apex was attached by a short stout band. Senac curtly dismisses the report of "three green stones" found in the cavity by Lancisi as insignificant, merely adding to the number of rare diseases, "taches blanches," on the other hand, he found to be common "Stone" or "ossified" hearts had been described by various early writers before Senac, though obviously, without the aid of the microscope, the composition of the hardened masses remains in doubt Haller's case in a young man with associated similar changes in the valves would today suggest a rheumatic origin (Figure I-13). Allusion has already been made to the importance of the English school in establishing this connection. On etiology and pathogenesis, as is to be expected, Senac is far weaker, though he did recognize pneumonia and pleurisy and other infections as frequent causes of pericarditis Little more was added to the knowledge of pericardial diseases until developments in cellular pathology made possible more exact identification of tuberculosis, secondary neoplasms, and other conditions, and bacteriology elucidated much of their etiology It is evident that the constrictive element of chronic adhesive pericarditis was recognized by Lower (1669), by Lancisi, and by Morgagni (1761), in one of his chronic cases It was overlooked, however, for more than a century, in spite of the clear descriptions by Chevers (1842), Greisinger (1854, recorded in 1856), Wilks (1870) and Kussmaul (1873). It was not until 1896 that Friedel Pick's article on pericarditic pseudocirrhosis brought general recognition of this variant; a condition which, regardless of its etiology, was

224 OPUSCULA

OBSERVATIO LII.

Lapis in corde (h).

SEd meretur inprimis enormis morbus posteris memorari, quo egregius juvenis haud ita dudum exstinctus est. Matre natus, ut ex medico clinico percepi, obnoxia palpitationibus cordis, ante octo annos, ephebus tunc, in simile malum inciderat. Ipse ea die vocatus, qua interiit, absque pulsu, quem in carpo tangeres, reperi, ut tamen carotides vehementer subsilirent. Frigido jam sudore madentem tristi prognostico invitus reliqui. Paulo post exstinctum corpus aperuimus. Pericardium cordi, pulmo pleurae passim adnatus, & in tota superficie pericardii passim scirrhi albi, alii duri, alii alba materie puris simili pleni fuerunt. Eorum scirrhorum ope cor cum pericardio uniebatur, irresolubili omnino vinculo. Ventriculi dextri pars inferior semilapidea, calculi tophacei ex arenulis congesti ope cum pericardio cohaesit. Sinus inter duas membranas valvularum aortae callosi & partim lapidei fuerunt. In valvulis aortae inter membranas materies sabulosa erat, tendines

(h) [illegible], 1751.

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dines vero, qui eas valvulas retinent, pulposi denique & ossea squamulis varii reperti sunt. Sed praecipuum malum in valvulis venae pulmonalis latuit. Eae totae durissimae & solidissimae fuerunt, ita calculosa materie plenae, ut passim dissectis fibris creparent. Sinus etiam pulmonalis caro lapidosa materie facta fuit. Neque cor, neque vasa magna molem solitam excesserunt. Raritatem mali ipsa aetas viginti annorum auxit. Non clausum autem hujus juvenis cor; neque satis apertum, caruit alterna requie, sine qua ne ipsum cor quidem esse potest. Nam sinister ventriculus, & aegre sanguinem a sinu sui lateris recipiebat, & in ipsa contractione sua per hiatum immutabilem osseatum valvularum mitralium remittebat ad eum sinum. Ita ex aorta pariter sanguis inter inexplicabiles rigidasque valvulas aortae in cor redire potuit. Unde, cum cor perpetuo stimularetur, palpitavit perpetuo, & cum cerebro sanguinis satis mittere non posset, ejusmodi soporis causa fuit, qualis ex defectu cruoris, a venae sectione & a vulneribus ferreus ingruit.

I 4 OBSER-

Figure I-13 Haller's description of calcification of the pericardium and aortic valves (From his *Opuscula Pathologica*, 1755.)

important because of its prognostic individuality and because it was soon to be demonstrated as amenable to surgical relief. *Pericarditis as a complication of myocardial infarct* was recognized by C Bäumler (1872) and V. Vernig (1892), but not well appreciated before M. Sternberg's description of *Pericarditis epistenocardica* (1910).

Endocardium. Examples of diseased valves like those of other parts already mentioned, accumulated sporadically, along with the gradual establishment of the anatomic concept of disease. A lesion of the tricuspid, the most resistant valve of the four, was one of the earliest described — by Lower (as cited by Bonetus), and by Senac who cites Haller and several others, Vol 2, p. 403, in the 1789 Edition). Senac, however, recognized that the semilunar valves were more frequently involved than the "auricular" Thickening and incompetency of the aortic valves was well described and illustrated by Cowper (1706) and by several of the British school a century later, among others Hodgkin (1827) and Corrigan (1832) who had an especially good comprehension of its functional results, as is worthily perpetuated in "Corrigan's pulse." Mitral stenosis was known to Vieussens (1715), who also recognized a resultant dilatation of the left atrium with a small, weak pulse, damming of blood in the lungs and hyper-

trophy of the chambers of the right side.

The concept of endocarditis, even the name itself, is ascribed to J. B. Bouillaud (1796-1881, Figure I-14), whose *Traité Clinique des Maladies du Coeur* (1835) gave a much clearer picture of the disease than had hitherto existed. However, this falls far short of Trousseau's extravagant statement that it was "a description to which nothing could be added."* Bouillaud considered three stages: a period of congestion and ulceration or suppuration, a second stage of organization of secretions or fibrinous concretions, and a third stage of endocardial induration with or without valvular stenosis. This third stage, which is easy enough to see, was known for over a century, as has just been described. The first, in part recalling the congestive beginning of any inflammation, was largely theoretical yet persisted into twentieth-century teaching, while the ulceration clearly indicates a malignant form, "as the ancients would have called it" (Bouillaud). The second period, that of organization, is found to refer both to fibrinous, easily removed vegetations (the "globular vegetations" of Laennec) and to resistant "verrucous vegetations" or "cornified excrescences." Here is a confused mixture largely based, as Bouillaud states, on Laennec, though Bouillaud's concept of its pathogenesis hits nearer the mark than does Laennec's

Acute endocarditis was first clearly differentiated at a considerably later period, the clue to its nature being indicated by Samuel Wilks' report on *Arterial Pyemia* (1870). Our present term, "acute bacterial endocarditis," followed isolation of methods for identifying bacteria. The distinction of the much commoner subacute bacterial endocarditis was established on the basis of its slower course and its fre-



Figure I-14 Jean-Baptiste Bouillaud (1796-1881) (From an original *carte de visite* photograph at College of Physicians of Philadelphia)

quent association with a nonhemolytic streptococcus, as the bacterium is now called (See Schottmueller, 1903.) Recognition of this variety in America owes much to Osler (1909), and Libman (1910, 1912), who stressed its regular occurrence on previously damaged tissue and its slow but invariably fatal termination, a condition now happily changed by the antibiotics The endocarditis of lupus erythematosus disseminatus has been too recently isolated and delimited to be properly included in this survey.

Myocardium. Lesions of the myocardium, being in general less striking than those of the other two cardiac layers, took longer to be adequately recognized and classified. Its importance, however, has been appreciated for more than a century: "It is in the vital and anatomical condition of the muscular fibres that we find the key to cardiac pathology," in the words of William Stokes (1804-78), the distinguished *Irish physician who* described Cheyne-Stokes respiration and Adams-Stokes *syndrome* (heart block). It took the man-

* A fair and discriminating consideration of Bouillaud and his contributions to cardiology is to be found in Herrick's History



Figure I-15. Sir James Mackenzie (1853-1925) Portrait by Allan Barr (Courtesy of Army Medical Library, Washington 25, D C, Neg No 50068)

power needs of a world war and the persistent acumen of Sir James Mackenzie (Figure I-15) to force the realization that valve murmurs in themselves were significant only when accompanied by limitation of the functional capacity of the myocardium.

Of the localized lesions of the heart muscle, cases of abscess and ulcer had been rather vaguely described from Bonetus on, and this cause is still carried "on the books" as a cause of rupture. Laennec cites Bonetus (*Sepulchretum*, Bk. 2, Sect. 1, Obs. 86), Morgagni and Senac as having collected many cases of ulcer of the interior surface, his single example caused a rupture of the ventricle – "a very rare accident almost always the result of ulceration of the ventricular parietes." True fatty degeneration, in the sense of "an actual transformation of the muscular substance into a substance possessing most of the chemical and physical properties of fat" was recognized by Laennec, though only "in a small portion of the heart at one time" Without the aid of the microscope, he had to rely on such crude evidence as the appearance of a spot of grease on a piece of folded paper within which suspect muscle had been compressed. He distinguished this condition from "simple softening" (myomalacia of Ziegler) and never found rupture attributable to it, though the confusion to the naked eye of fatty degeneration with necrosis led to the former being wrongly regarded as an important cause of rupture until well into the twentieth century (See earlier discussion under Cardiac Rupture.)

Myocarditis, a term used by Sobernheim in 1837, was recognized as being either acute or chronic – the former applied well enough to suppurative forms and even to the nonsuppurative forms, after microscopic criteria for inflammation had been established. Even Virchow's insistence on parenchymatous inflammation and inflammation of the single cell had to give way to the parenchymatous degenerations elaborated by Weigert, Zenker, Ziegler, and others. Chronic myocarditis presented a more difficult situation Were the pale, hard areas of the indurated heart of early days – the connective or fibrous tissue areas of the later nineteenth century – signs of an inflammation starting in the heart muscle, as Bouillaud, Kreysig, Hope, and Rokitansky maintained? Or did they start as an inflammation in the interstitial tissue (Meckel, Corvisart)? Or were they not inflammatory at all, but manifestations of a sclerosis due to complete or partial obliteration of the coronary branches – scars of an ischemic necrosis? Ziegler came nearest to the correct answer with his

theory that myomalacia, the acute softening of necrosis, was caused by rapid thrombosis, and sclerosis by slow thrombosis Weigert had a still better version of the pathogenesis when he added to the causative progressive obliteration of coronary branches the general concept of replacement fibrosis in parenchymal tissue Yet "chronic interstitial myocarditis" still remains the preferred term in a few pathologic, and more clinical, textbooks – a usage that is unjustified except occasionally in connection with rheumatic carditis, and rarely in syphilis.

The pathologic anatomy of the heart in thyroid disease need not detain us, as the findings in both toxic goiter and myxedema are trivial, inconstant or of obscure genesis.

Similarly, with one exception, the various arrhythmias have no describable lesions Defective conduction, however, unless due to toxic, drug or neural factors, is found to be linked with lesions in the A-V conductive system.* Shortly after the rediscovery of the bundle of His, Joseph Erlanger, at Osler's suggestion, produced complete block by experimental compression of the bundle (1905) and, even before the original discovery of the bundle, Gaskell (1883), Wooldridge (1883) and Tigerstedt (1884) had shown that compression of the atrioventricular groove would cause dissociation of the A-V rhythm Also in 1905, A. Stengel reported a case of complete block due to an atheromatous calcified area lying in and on the main trunk of the bundle In rapid succession, cases were found that were attributed to fibrosis (the commonest cause), syphilis, fatty degeneration of the muscle of the bundle, fatty infiltration with compression, sclerosis and calcification and thrombosis of the nutrient artery Very few carefully studied cases have been reported in which complete block was not found to be associated with an adequate lesion of the His bundle.

* His, who in 1893 discovered the muscle bundle that still bears his name, two years later found experimentally that A-V dissociation was due to damage to the bundle This, however, like his anatomical discovery, lay dormant for a whole decade

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CHAPTER II

The Development of the Heart

Bradley M. Patten

THE PLAN OF THE EMBRYONIC CIRCULATION AND ITS FUNCTIONAL SIGNIFICANCE

Any account of the prenatal development of the heart which is limited to an entirely morphologic approach inevitably will be disappointing as a basis for understanding cardiac physiology or pathology. The embryonic heart can be intelligently studied only in relation to its changing functional rôle as the plan of the embryonic circulatory system is altered during development. It is unnecessary to be concerned, in most instances, with peripheral vessels, but the changes in the main blood streams that enter and leave the heart must be borne clearly in mind in order to understand the structural changes occurring in the heart itself. If one uses as a basis of approach certain fundamental conceptions as to the significance of the circulatory system in organic economics, and the evolutionary principle that any embryo must go through certain ancestral phases of organization before it can arrive at its adult structure, the changes in the arrangement of vascular channels and the different routings of blood through the heart during the course of development will then form a coherent and logical story.

In the embryo, as in the adult, the main vascular channels lead to and from the centers of metabolic activity. The circulating blood carries food from the organs concerned with its absorption to parts of the body remote from the source of supplies; oxygen to all the tissues of the body from organs that are especially adapted to facilitate the taking of oxygen into the blood; and waste materials from the places of their liberation to the organs through

which they are eliminated One of the primary reasons the arrangement of the vessels in an embryonic mammal differs so much from that in the adult is that the embryo lives under conditions totally unlike those which surround its parents. Its centers of metabolic activity are, therefore different; and, since the course of its main blood vessels is determined by these centers, the vascular plan is different

The organs which in the adult mammal carry out such functions as digestion and absorption, respiration, and excretion are extremely complex and highly differentiated structures. They are for this reason slow to attain their definitive condition and are not ready to become functional until toward the close of the embryonic period. Moreover, the conditions which surround certain of the developing organs during intra-uterine life absolutely prevent their becoming functional even were they sufficiently developed to do so. Suppose the lungs, for example, were functionally competent at an early stage of development. The fact that the embryo is reliving ancestral conditions in its private amniotic aquarium renders its lungs as incapable of functioning as those of a man under water Likewise, the developing digestive organs of the embryo are inaccessible to raw food materials Further examples are not necessary to make it obvious that, were the embryo dependent on the same organs that carry on metabolism in the adult, development would be at an impasse.

An embryo must, nevertheless, solve the problem of existence during the protracted time in which it is building up a set of organs similar to those of its parents In the absence of a dowry of stored food in the form of yolk, the mammalian embryo draws upon the uterine circulation of the mother. Utilization of this source of supplies depends on the development of a special organ which serves through fetal life and is then discarded The embryo takes food not into its slowly developing gastrointestinal tract but into its chorion, a membrane projected outside its own body and applied to the inner lining of the uterus to form the placenta. The nutritive materials there absorbed from the maternal blood must be transported to the growing embryo by its own blood stream

The use of food materials to produce the energy expressed in growth depends on the presence of oxygen. For growth there must be a means of securing oxygen and carrying it, as well as food, to all parts of the body Nor can continued growth go on unless the waste products liberated by the developing tissues are eliminated The blood of the embryo cannot be relieved of its carbon dioxide and acquire a fresh supply of oxygen in the primordial cell clusters that will later become its lungs It cannot excrete its nitrogenous waste products through undeveloped kidneys Its respiration and excretion, like its absorption of food, are carried out in the rich plexus of small blood vessels in the chorion. Here the fetal blood is separated from the maternal by tissues so thin that it can readily give up its waste materials to, and receive food and oxygen from, the maternal blood stream, just as the mother's own tissues constantly carry on this interchange with the circulating blood The placenta is thus the temporary alimentary system, lung, and kidney of the mammalian embryo The enormous chorionic blood supply during fetal life, and the entire disappearance of this special arc of the circulation when the organism assumes adult methods of living, is a very striking example of the determination of vascular channels by the location of functional centers. We must not, however, overlook the fact that there are many other centers of activity in the growing embryo less conspicuous but equally important for its continued existence. Each developing organ

tense metabolic activity. During fetal life it must be supplied by vascular channels adequate to care for its growth.

But that is not all. Up to the time of birth each organ has been drawing on blood furnished with food and freed of waste materials by the activities of the maternal organism At birth all this must change. Each organ essential to metabolism must be ready to assume its own active share in the process Their vessels must be adequate to take care, not only of the needs of these organs, but also of the new functions these organs assume in maintaining the metabolism of the organism as a whole.

While the functional significance of the arrangement of the blood vessels is of primary importance, especially in understanding the progressive changes in vascular plan, there is another factor which we cannot overlook. This factor is conservative, having to do with the things we inherit from our forebears. The goal of the embryonic period is the attainment of a bodily structure similar to that of the parents Because it is so familiar, we accept with complaisance the remarkable fact that this goal is attained with absolute regularity. Accidents there may be, leading to defective development or malformation, but the fertilized ovum of one species always gives rise to an individual of that species and to no other. The new individual will show detailed differences from its parents, differences which are capitalized in the slow march of evolution, but in a single generation these differences are never radical. We say that the offspring has inherited the structure of its parents. It does more, it inherits the tendency to arrive at its adult condition by passing through the same sort of changes which its ancestors underwent in the countless millions of years it took their present structure to evolve.

Applied to the development of the circulatory system of the human embryo this means that the earliest form in which it appears will not be a miniature of the adult circulation. The simple tubular heart pumping blood out over aortic arches to be distributed over the body and returned to the posterior part of the heart by a bilaterally symmetrical venous system – in short, the vascular plan which we see in young mammalian embryos (Figure II-15) – is essentially the plan of the circulation in fishes. When we realize this, we are not puzzled by either the appearance of a full complement of aortic arches or their subsequent disappearance to make way for a new respiratory circulation in the lungs We see the march of progress from a logical beginning in ancestral conditions toward the consummation of fetal life with an organization like that of the parent.

In addition to the fundamental ground plan of the circulation of the mammalian embryo, recapitulations account for many transitory peculiarities. The formation of a conspicuous, though empty, yolk-sac with a complement of blood vessels almost as well developed as the vitelline vessels of animals well endowed with yolk is clearly a recapitulation of ancestral conditions. So, also, is the highly developed system of venous channels in the mesonephros. If the organ itself appears, it brings with it its quota of vessels, no matter if the organ is destined to degenerate later in development.

Whatever peculiarities may be impressed on the course of the circulation by the appearance of ancestral structures, or by the development of special fetal organs such as the yolk-sac and the placenta, the main blood currents will at any time be found concentrated at the centers of activity. Changes of these main currents as one center retrogresses and another becomes dominant must take place gradually. Large vessels become smaller, what was

formerly an irregular series of small vessels *becomes excavated to form a new main* channel, but the circulation of blood to all parts of the body never ceases. Even slight curtailment of the normal blood supply to any region would stop its growth, any marked local decrease in the circulation would result in local atrophy or malformation, complete interruption of any important circulatory channel, even for a short time, would inevitably mean the death of the embryo.

THE ESTABLISHING OF THE PRIMARY EMBRYONIC CIRCULATION

The human embryo, having practically *no yolk available as food, is dependent for* its survival and growth on the prompt establishment of relations with the circulation of the mother This implies the necessity of a precocious development of the vascular system of the embryo, for the maternal circulation remains confined within the uterine walls and the embryonic circulation must grow to it. Until this is accomplished the embryo is dependent on what food material it can obtain from the uterus by direct absorption – a method entirely inadequate to provide for its growth except in very early stages when the bulk of the embryo is inconsiderable.

The Cardiopericardial Primordium. The primordial tissue aggregation which is the precursor of both the heart itself and the lining of the primitive pericardial region of the coelom is a crescentic zone of thickened mesoderm (Davis, 1927). This zone first becomes clearly defined in human embryos in the primitive streak stage (fertilization age about 15 days). It is located in front of the embryonic disk and swings around to either side, following the curvature of the cephalic *margin of the disk* (Figure II-1A). When this thickened mesodermal area first becomes recognizable it is not yet split into splanchnic and somatic layers (Figure II-2A). Even in this very early stage, in forms such as the chick which lend themselves to experimental procedures, it is possible to demonstrate the cardiogenic potentialities of cells within this area by explanting them and allowing *them to differentiate as* grafts on the chorio-allantois of older chicks Under such circumstances the cells in question will develop myofibrils and clearly declare their myocardial potencies by their rhythmic pulsation

A day or two later than the primitive streak stage the thickened zone of mesoderm becomes split into somatic and splanchnic layers, thereby establishing vesicular spaces which soon coalesce to make a cavity which is destined to be the pericardial part of the coelom (Figures II-1B and II-2B) Concurrently, the head of the embryo has been growing rapidly *so it has pushed out over the newly formed* pericardial coelom (Figure II-2B, C). At the same time the pericardial part of the coelom is extended by further splitting of the mesoderm, so that it sweeps back on either *side of the body following the curve* of the foregut (Figure II-1C)

The Formation of the Heart. Once the pericardial cavity is thus established, one can drop the cumbersome term "cardiopericardial primordium" and speak of the *cardiac primordia* which take shape at specific locations within this general area The cardiac primordia are formed from the splanchnic mesodermal layer of the *primitive pericardial cavity, on either side,* where it lies close against the developing foregut (Figures II-2C and 3A). The fact that the heart, a median unpaired structure in the adult, arises from paired pri-

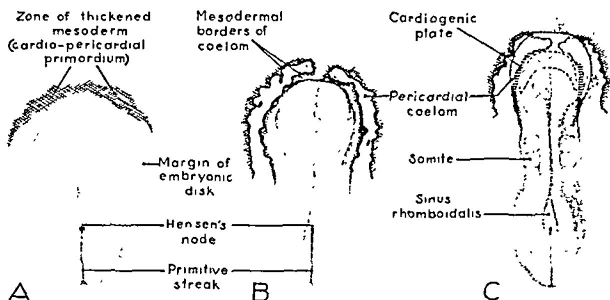


Figure II-1 Diagrams showing the location of the cardiopericardial primordia in embryos early in the third week of development The cross-hatched area in A represents the zone of thickened mesoderm before the formation of coelomic cavities The light areas in B and C represent the coelomic cavities as if they were seen through a semitransparent embryonic body The broken lines in C show the position of the foregut (Based in part on the work of Davis *Carnegie Contrib to Embryol*, Vol 19, 1927)

mordia which at first lie widely separated on either side of the midline is correlated with the fact that the embryonic body at first is open ventrally and lies spread out prone on the surface of the yolk-sac. The primordia of certain anatomically ventral structures arising at an early stage of development, therefore, first appear as separate halves lying on either side of the midline. With the folding under of the lateral margins of the embryonic area, which brings the ventrolateral walls of the body into their definitive position, the embryo is closed ventrally, and potentially midventral structures which arose as separate halves are established in the midline.

The primordial heart is double-layered, as well as paired right and left. The inner layer is called the *endocardium* because it is destined to form the internal lining of the heart. The outer layer is known as the *epimyocardium* because it will give rise both to the muscular layer of the heart wall and to its epicardial investment.

The endocardium, when it first appears, is in the form of irregular clusters and cords of mesenchymal cells lying between the splanchnic mesoderm and the entoderm (Figure II-3A). These cells become organized into two main strands, lying one on either side of the gut. Soon after their establishment, the strands acquire a lumen and are known as the *endocardial tubes* (Figure II-3B). The endocardial tubes continue beyond the cardiac region as branching strands which will become, cephalically, the primitive ventral aortic roots and, caudally, the veins entering the heart (Figure II-4A). The splanchnic mesoderm soon becomes markedly thickened where it is reflected laterally over the endocardial tubes to constitute the epimyocardial layer of the heart (Figure II-3B).

Meanwhile, folding-off of the embryonic body continues with concomitant progress in the closure of the foregut at the level of the heart. As a result, the paired endocardial tubes are brought progressively closer together Finally, they are approximated to each other and fuse to form a single tube lying in the midline (Figures

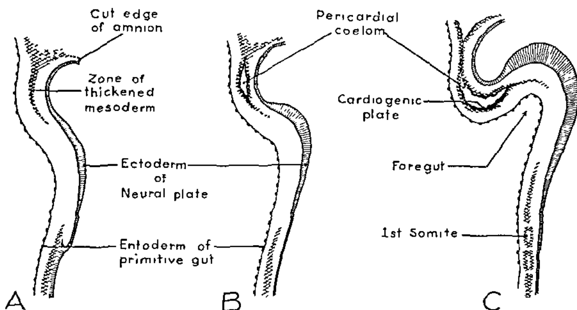


Figure II-2 Longitudinal sections of embryos early in the third week of development showing the way the cardiopericardial primordium, which at first lies in front of the cephalic margin of the embryonic disk, is overridden by the forward growth of the head As the foregut is formed within the head, the cardiopericardial primordium is turned under it and extends back on either side, flanking the anterior intestinal portal (Based in part on the work of Davis *Carnegie Contrib to Embryol*, Vol 19, 1927)

II-3C, D and II-4B). In the same process, the *epimyocardial layers* are bent mesially, completely enwrapping the endocardium Ventral to the heart, the mesodermal layers of the opposite sides of the body become continuous with each other so that, in the same process which establishes the heart as a median structure, the originally-paired right and left coelomic chambers become confluent to form a median pericardial cavity (Figure II-3C, D) Dorsally, the right and left epimyocardial layers become contiguous, but here they do not fuse immediately, as happens ventral to the heart. They persist for a time as a double-layered supporting membrane called the *dorsal mesocardium*. In this manner, the heart is established as a nearly straight, double-walled tube suspended mesially in the most anterior part of the coelom

Cardiac Jelly. Even at this early stage, interesting histogenetic changes are beginning to become apparent. The endothelial nature of the endocardial primordia is clearly evident in the configuration of their constituent cells, and in the littoral relation of the cells to the developing lumen of the heart. This inner endothelial layer of the cardiac tube is held in relation to the outer, epimyocardial layer by a gelatinous substance called *"cardiac jelly"* (Davis, 1927). The cardiac jelly is so translucent and structureless that it is easily overlooked unless one observes the mechanical evidences of its presence in living material If a beating embryonic heart in the tubular stage is transected, one sees the endothelial layer follow every movement of the pulsating epimyocardial sleeve which encloses it (Patten, Kramer and Barry, 1948). In the absence of any internal fluid pressure, this can be accounted for only on the basis of the supporting and cohesive action of the cardiac jelly between these two layers (Barry, 1948).

In its fixed condition cardiac jelly appears as a delicate meshwork of coagulated material, at first entirely devoid of cells

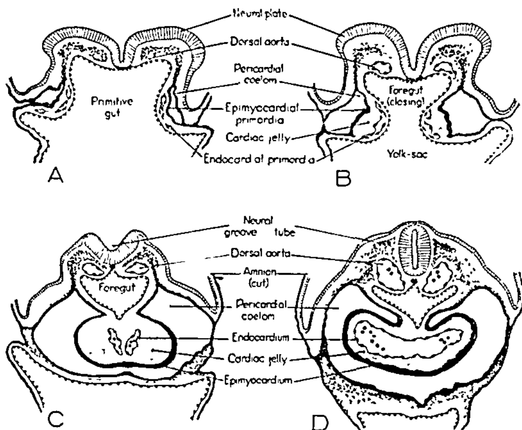


Figure II-3 Four stages in fusion of paired primordia of heart as seen in cross embryonal sections A Based on the Ludwig, two-somite embryo B. Based on the Carnegie 3709, four-somite embryo C Based on the Payne, seven-somite embryo. D Based on the Corner, 10-somite embryo. (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

(Figure II-5A). As development progresses cells, apparently arising from the endothelium, invade the cardiac jelly and become organized into the primitive plastic type of connective tissue which is commonly called *endocardial cushion tissue* (Figure II-5B and C). Local masses and ridges of this endocardial cushion tissue we shall see playing an important rôle in the partitioning of the heart and in the molding of its valves. In the areas not so specialized, thin layers of this same tissue form the subendothelial connective tissue stratum of the adult endocardium.

Histogenesis of Cardiac Muscle. The mesothelial character of the cells which constitute the layer of the epimyocardium adjacent to the pericardial cavity is, from the first, quite evident (Figures II-5 and II-6A). The inner part of the epimyocardium gives rise to the muscular tissue of the cardiac wall. In the early stages of their differentiation, the cells of the myocardium are packed closely together with little indication of any definite plan of arrangement. About the time the first contractile activity begins, the nuclei are somewhat less close together and the cytoplasm of adjacent cells has coalesced to form a loose, irregular syncytium. It is at about this time, also, that a suggestion of the formation of myofibrils begins to be recognizable.

Not long after their first appearance, the young myofibrils become conspicuous They are much larger than the fibrils of more mature cardiac muscle and show definite dark bands due to the local concentration of anisotropic substance (Figure

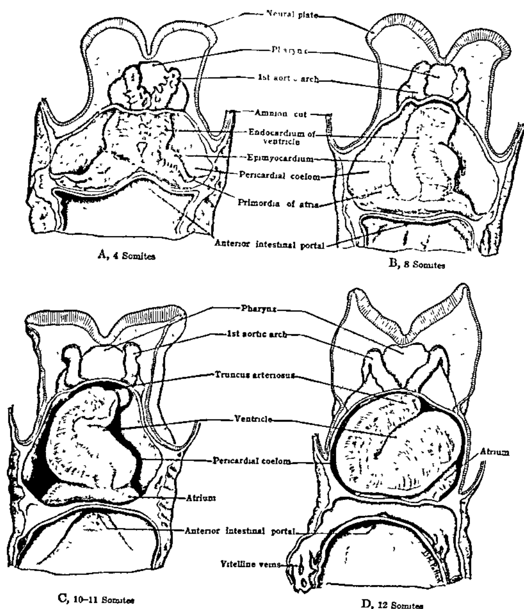
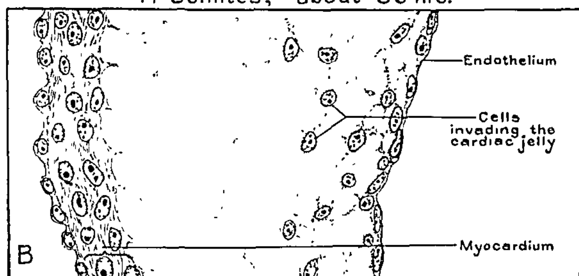


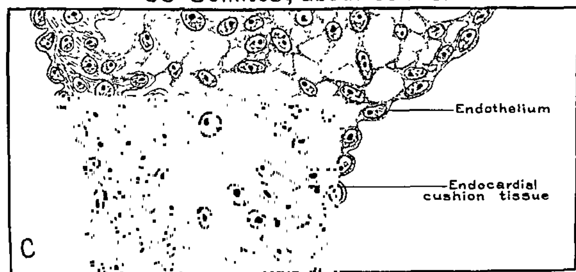
Figure II-4 Four stages in formation of heart exposed by ventral dissection (Based on the figures of Davis, *Carnegie Contrib. to Embryol*, Vol 19, 1927. From Patten, *Human Embryology*, courtesy of The Blakiston Company)



14 Somites, about 36 hrs.



33 Somites, about 65 hrs.



40-41 Somites, about 84 hrs.

II-6B). At this early stage the myofibrils are relatively few in number and they pursue a startlingly irregular course frequently crossing one another. They traverse the syncytium for considerable distances, certainly not being restricted to any limited cytoplasmic areas such as might have been derived from single cells before their coalescence.

The later stages in the histogenesis of cardiac muscle are along the lines one would expect from a knowledge of its adult structure. As the growing muscle is pulled into spiral bands about the developing chambers of the heart, the strands of the syncytium gradually become less irregular in their arrangement. In the sectioned material from the hearts of embryos of the third month, areas appear showing groups of fibers running more or less parallel to each other and crossing other groups of fibers at varying angles. The myofibrils have become more abundant, and lining up of the dark and light portions of adjacent fibrils is beginning to give the muscle a cross-striated appearance (Figure II-6C). In comparing fetal with adult cardiac muscle the further increase in the number of myofibrils and their decrease in coarseness is most striking (cf. C and D in Figure II-6).

The last of the characteristic histologic features of cardiac muscle to make their appearance are the intercalated disks. These curious transverse markings seem to appear about where one could readily believe adjacent cellular elements fused to form the syncytium, but with cardiac muscle having been syncytial almost from its establishment, the concept that these disks really do represent the re-emergence of the original cell boundaries is difficult to support.

Primary Regional Divisions of Heart. Returning from the consideration of histogenetic changes to the general configuration of the growing heart, we find that very early in development the dorsal mesocardium disappears except for a persistent portion at its caudal end (cf. Figures II-29A and B). Thus the tubular heart comes to lie in the pericardial cavity, attached only cephalically where the ventral aortic roots branch out into the tissue beneath the foregut, and caudally where the great veins enter (Figure II-7). Being unattached in its mid-portion, it is free to change its shape and position and, since it grows much more rapidly in length than does the pericardial part of the coelom in which it is situated, the originally straight heart tube soon becomes conspicuously bent (Figures II-4C and D and II-7).

With the elongation and bending of the cardiac tube, its primary regional divisions begin to be recognizable. Naming them in the order they are traversed by the circulating blood, these regions are the sinus venosus, the atrium, the ventricle, and the truncus arteriosus (Figure II-8). The *sinus venosus* is a thin-walled chamber formed by the confluence of the great veins entering the heart (Figure II-29C). Since the fusion of the cardiac primordia begins at their cephalic ends and progresses caudad, the sinus venosus is the last part of the heart to be established and at early stages shows but slight differentiation.

← Figure II-5 Drawings showing stages in the cellular invasion of cardiac jelly with the resultant formation of endocardial cushion tissue. All the drawings were made from comparable areas in the conotruncus to the same scale (original X 1000, reproduced X 750) (From Patten, Kramer and Barry, *Anat Rec*, Vol 102, 1948)

A From a 14-somite chick (± 36 hours), showing the primary non-cellular character of the cardiac jelly. Note the thinness of endothelium except for the place indicated by the arrow.

B. From a 33-somite chick (± 65 hours), showing the beginning of cellular invasion. Note the thickened character of the endothelium and that cells have not as yet reached the myocardium.

C. From a 40 to 41-somite chick (± 84 hours), showing cells throughout the territory formerly occupied by the cardiac jelly alone.

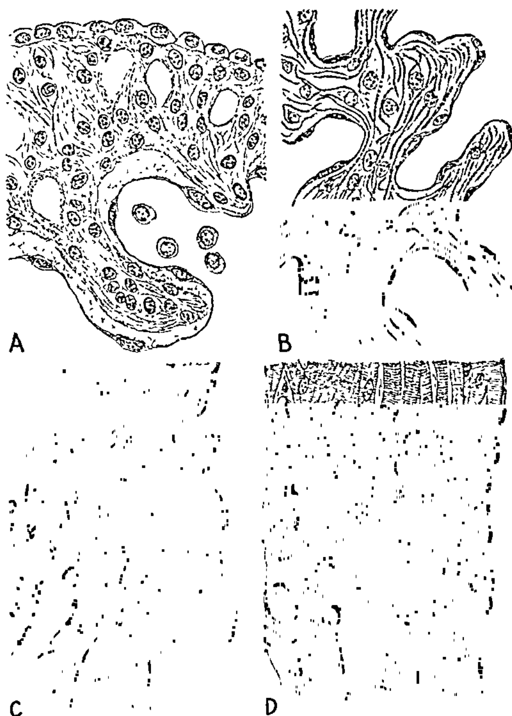


Figure II-6 Histogenesis of cardiac muscle (Camera lucida drawings, X 500) A Entire thickness of ventricular wall of 4.5-mm embryo B Developing trabeculae from inner part of ventricular wall of 9-mm embryo C. Inner part of ventricular wall of 45-mm embryo D. Inner part of adult right ventricular wall (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

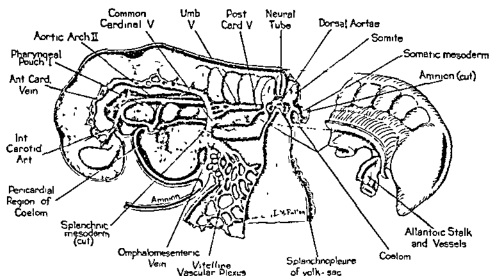


Figure II-7. Schematized lateral dissection of human embryo of about three weeks, to show continuity of pericardial portion of coelom with paired coelomic chambers of midbody region (*Based, in part, on Heuser's study of a 14-somite embryo, Carnegie Coll., 4529 From Patten, Human Embryology*, courtesy of The Blakiston Company)

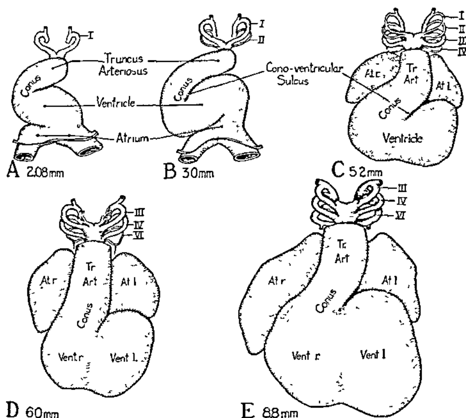


Figure II-8 Ventral views of human embryonic hearts, to show bending of cardiac tube *and establishing of regional divisions* (After Kramer, *Am J Anat*, Vol 71, 1942)

From the sinus venosus the blood passes into the atrium. Guarding the slitlike orifice between these two chambers against the return flow of blood are well-developed flaps known as the valvulae venosae (Figures II-16 and II-18) The *atrial region*, soon after it is established, undergoes extensive transverse enlargement so that it bulges out into pouchlike right and left chambers (Figure II-8). Although the beginning of the separation of these chambers from each other is clearly indicated as early as the fifth week by the presence of an interatrial septum, this septum is not immediately completed and the atrial chambers remain for a time in communication caudally by way of an opening called the primary interatrial foramen or, more briefly, ostium I (Figures II-16 and II-28 B, C).

Leaving the atrium, the blood passes to the ventricle through a constricted region known as the *atrioventricular canal*. The *ventricle* is formed from the most sharply-bent part of the cardiac tube (Figure II-4C and D). Correlated with its activity in pumping, the ventricular wall becomes greatly thickened, with irregular branching bands of developing muscle tissue protruding from the main part of the wall into the lumen (Figure II-6A). These primordial trabeculae carneae already suggest the muscular bands which project so characteristically into the cavities of the adult ventricles From the ventricle the blood passes into the *truncus arteriosus* and thence out to the body by way of the ventral aortic roots.

It should not be inferred from the modifications which have occurred in the different regions of the heart that it has as yet altered its primitive method of functioning. The heart tube becomes bent and shows local dilations and constrictions which we are able to name because we know their future fate. Many internal conditions point toward its division into right and left sides. But the blood in the early stages of development enters the heart dorsally by way of the sinus venosus, is collected in the atrium, and passes into the ventricle whence it is pumped out by way of the truncus arteriosus as an undivided stream.

The Primary Arterial Channels. While these changes have been occurring in the cardiac region, the main vascular channels characteristic of young embryos are making their appearance (Bremer, 1914). The cephalic prolongations of the endocardial tubes beyond the cardiac region constitute the start of the main efferent channels or aortae. The aortae are further extended by a process similar to that involved in the formation of the endocardial tubes themselves. Cords and knots of cells of mesodermal origin become aggregated along the course of the developing vessel. These strands of cells are then hollowed out to form tubes, walled by a single layer of endothelial cells. Where main blood vessels are about to become established there is found first a meshwork of these small channels (Evans, 1909). Gradually, some of these primitive channels are enlarged and straightened to form the main vessels, and their walls are later reinforced by the addition of circularly-disposed connective-tissue fibers and smooth muscle cells. In this manner, the primitive efferent channels are prolonged from the heart cephalad, beneath the pharynx, as the ventral aortae. They then bend laterally and dorsally about the pharyngeal walls to form aortic arches, and finally turn caudad to extend nearly the entire length of the embryo as the dorsal aortae (Figure II-15).

At first, there is but a single pair of *aortic arches* which is located in the tissue of the mandibular arch (Figure II-9A). Later in their development, vertebrate embryos in general tend to form five additional pairs of arches connecting the ventral and dorsal aortae (Figure II-10A).

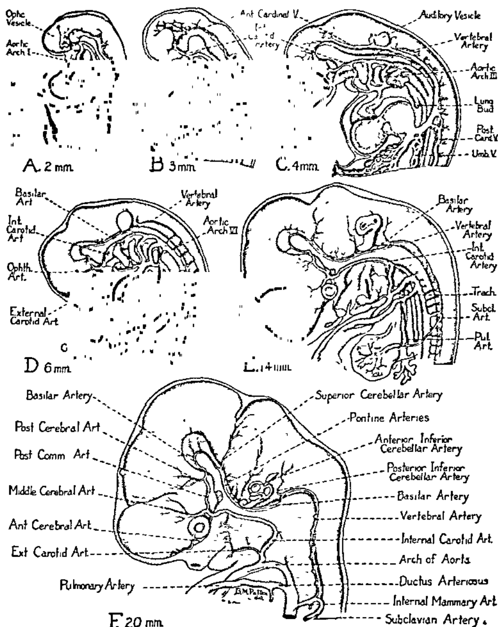


Figure II-9 Development of aortic arches and cerebral vessels in human embryos (Based, in part, on the work of Congdon, *Carnegie Contrib to Embryol*, Vol 14, 1922, from Patten, *Human Embryology*, courtesy of The Blakiston Company.)

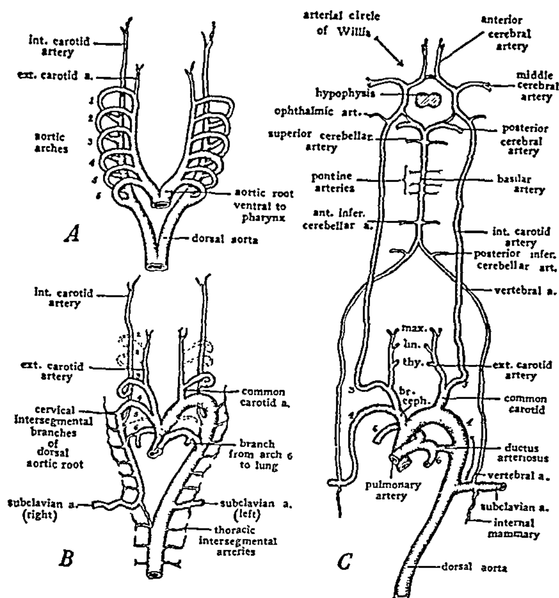


Figure II-10 Diagrams illustrating changes which occur in aortic arches of mammalian embryos (From Patten, *Human Embryology*, courtesy of The Blakiston Company) A Ground plan of complete set of aortic arches B Early stage in modification of arches C. Adult derivatives of aortic arches

Abbreviations br. ceph, brachiocephalic (innominate) artery, lin, lingual artery, max, maxillary artery; thy, thyroid arteries Figure II-9 shows from another view, and less schematically, some of the changes summarized in this illustration

The arrow in the lower part of C indicates the change in position of origin of left subclavian artery which occurs in the later stages of development

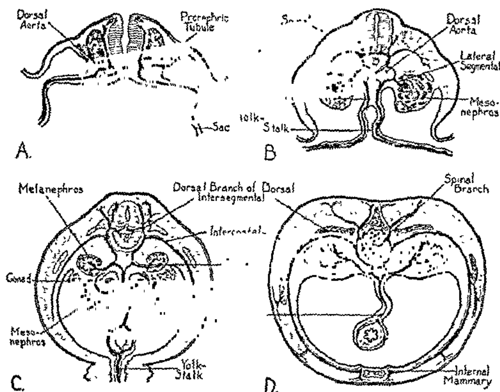


Figure II-11 Cross-sectional plans of the body showing relations of segmental branches of aorta at different stages of development (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

Each of these aortic arches lies in one of the visceral arches caudal to the mandibular The entire series of aortic arches, however, is never present at the same time in mammalian embryos, for the first two arches degenerate before all of the more caudal ones are formed, and the fifth is rudimentary and often wanting altogether (Congdon, 1922). From the functional standpoint, the significant thing is that blood passes by way of one or more pairs of aortic arches around the pharynx from the ventrally located heart to the dorsally located aortae which are the main distributing trunks of the embryonic circulation In human embryos of one month, the first three aortic arches are well formed and the fourth is usually just making its appearance (Figure II-15) By the time the embryo has reached a size of 10-12 mm., that is to say six weeks after fertilization, the first and second arches have degenerated and the aortic arches present are the third, fourth, and sixth of the series (Figures II-9 and II-10)

Throughout the length of the aorta, small branches appear at regular intervals and extend dorsad on either side of the neural tube Since these vessels are formed between adjacent somites, they are known as the *dorsal intersegmental arteries* (Figure II-15). Most of the important branches of the aorta arise either from these dorsal intersegmental vessels or from the other series of segmentally arranged branches which extend ventrally, and still others which extend laterally in the growing body (Figure II-11).

When first formed, the dorsal aorta is, as we have seen, a paired vessel (Figure II-11A). This paired condition is retained in the branchial region, but caudally the two primitive aortae soon fuse to form a median vessel (Figure II-11B, C). The fusion

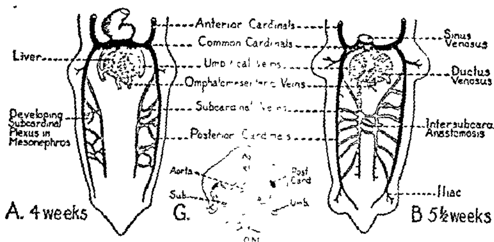
first occurs in the midbody region and extends thence cephalad to about the level of the anterior appendage buds and caudad throughout the length of the aorta.

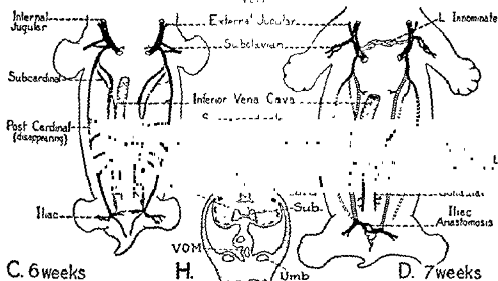
In young embryos, the most conspicuous vessels arising from the dorsal aorta ventrally are the *allantoic* or *umbilical arteries*, which supply the vascular plexus of the chorion, and the *omphalomesenteric arteries* which are prolonged as the vitelline arteries to the yolk-sac (Figure II-15). These vessels arise from the aortae before their fusion and, being derived by enlargement of its primitive ventral segmental branches at the levels concerned, are at first paired, right and left (Ingalls, 1920). The umbilical arteries retain their paired condition, but when the body is closed ventrally, the right and left omphalomesenteric roots are brought together in the midline and fuse to form a median vessel running in the mesentery (Figure II-11). With the early degeneration of the yolk-sac, this vessel becomes relatively less conspicuous and is known as the *superior mesenteric artery* (Figure II-11C, D). Its original relations are, nevertheless, apparent from its course along the intestinal loop into the belly-stalk to the place where the small yolk-sac still retains its attachment to the gut.

The Primary Venous Channels. The main vessels first serving to collect the blood which is distributed to all parts of the embryo by branches from the aortae are the cardinal veins. They arise by an entirely similar process, but become clearly defined somewhat later than the aortae. There are at first two pairs of these vessels, the *anterior cardinal veins* draining the cephalic, and the *posterior cardinal veins* draining the caudal region of the body. At the level of the heart the anterior and posterior cardinal veins on either side of the body become confluent as the *common cardinal veins*, or *ducts of Cuvier*. The common cardinals are short trunks which at once turn ventromesiad and enter the dorsal part of the heart (Figures II-12A and II-15).

Little alteration from primitive conditions occurs, at early stages, in the veins of the ventral part of the body. Numerous large tributary vessels appear, especially in the cephalic region, where they converge on either side of the head as the so-called *venae capitis*. It is already possible to recognize in the larger of these branches the primordial vessels from which the main venous sinuses of the adult cranial region are derived. Fundamentally, nevertheless, these veins are but an elaboration of the original anterior cardinal system.

In very young embryos, the posterior cardinal veins are the only conspicuous venous channels draining the caudal half of the body (Figures II-12A and II-15). By six weeks, however, new vessels have appeared and, while the relative position of the posterior cardinals as vessels lying dorsal to the mesonephroi remains unchanged, much of the blood formerly returned by them now reaches the heart by way of new channels. As a result, the posterior cardinal veins in the midmesonephric region begin to undergo regressive changes. The new vessels which thus bring about the diversion of the blood from the posterior cardinals are the *subcardinal veins* (Figure II-12C). When they first appear, these vessels are but an irregular plexus, tributary to the posterior cardinals (Figure II-12A). The organization of longitudinal channels in these plexuses establishes the main subcardinal veins as vessels extending cephalad in the ventromesial border of the mesonephroi, parallel with, and ventral to, the posterior cardinal veins. In the cephalic part of the mesonephros, the newly established subcardinal blood stream enlarges some of the small channels already entering the posterior cardinal and discharges through them into the posterior cardinal vein (Figure II-12B).





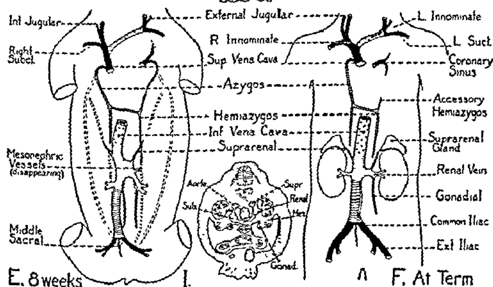


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With the growth of the mesonephroi the rapidly enlarging subcardinal veins are brought very close to each other. Where they are approximated, cross-communication is established, first by small vessels (Figure II-12B) and then by a broad *intersubcardinal anastomosis* (Figure II-12C, D). The large median *subcardinal venous sinus* thus formed probably offers less resistance to the flow of blood than surrounding channels, in any case, all the vessels connecting with it tend to drain toward it (Butler, 1927).

One might expect that the great volume of blood entering the subcardinal sinus would cause a corresponding enlargement of the cephalic portion of one or both subcardinal veins. Instead, a new and more direct channel toward the heart appears In its growth, the liver is crowded very close to the mesonephroi The developing liver contains a maze of vascular channels, as does the mesonephros Capillaries ramifying in the base of the mesentery between the liver and the mesonephros form the connecting link between the two organs Once the blood begins to find its way by this route, the small irregular channels are rapidly enlarged and straightened to form the primordium of the *mesenteric portion of the inferior vena cava* (McClure and Butler, 1925; McClure and Huntington, 1929, Reagan, 1929). The new and more direct channel thus established leads from the subcardinal sinus through the right subcardinal vein for a short distance, and thence, by the newly excavated channels in the mesentery, through the liver to the heart (Figure II-12B).

The venous return of blood from the yolk-sac circulation, and from the developing placental circulation also, secondarily, reaches the heart by way of the liver. At first the *omphalomesenteric veins* pass along either side of the yolk-stalk and the developing walls of the gut-tract to enter the sinus venosus directly (Figure II-13A). The growing liver, however, soon encroaches on their proximal portions so that instead of being returned to the heart by the original main veins, the blood is routed through a maze of small channels *ramifying among the developing cell cords* of the liver (Figures II-9B-D and 13B, C) Leaving the liver, the blood of this circuit is recollected to join the stream coming back from the body by way of the developing inferior vena cava (Figure II-13C, D)

The *umbilical veins* which return the blood from the chorion to the heart are, at first, paired vessels traversing the belly-stalk and the lateral body-walls of the embryo (Figure II-15). Their original direct course through the body-walls to the sinus venosus does not, however, long persist As was the case with the vitelline circulation, the growing liver interrupts the *umbilical veins* *The underlying factor in this* process is the extensive growth of the liver which brings it into contact with the lateral body-walls in which the umbilical veins are embedded Fusion follows the contact and small vessels develop between the umbilicals and the network of channels in the liver (Figure II-13B). As these new vessels develop, the portions of the umbilical veins cephalic to them gradually drop out altogether and all the placental blood passes through the liver (Figure II-13C, D).

Shunting Mechanisms in Embryonic Circulation. With the completion of this change in the umbilical circulation, the liver has become the common path of return for both of the original extra-embryonic circuits and most of the intra-embryonic circulation of the posterior half of the body This mounting volume of blood returning through the liver and reaching the heart by way of the developing inferior vena cava is, of course, a major portion of the cardiac intake during intra-uterine life. The fact that the original bilaterally symmetrical relations of these incoming vessels

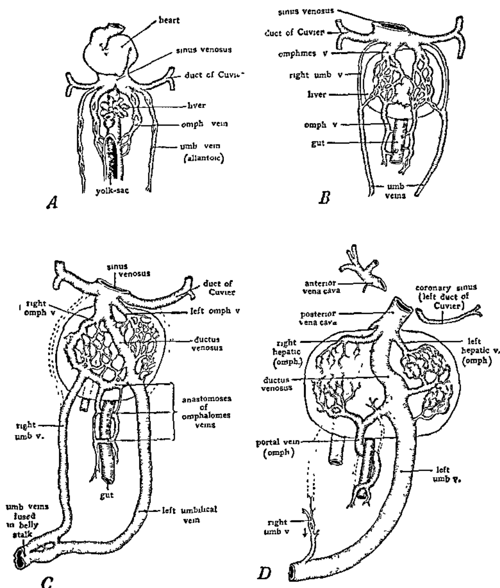


Figure II-13 Diagrams showing development of hepatic portal circulation from omphalomesenteric veins, and changes by which blood returning from placenta by way of umbilical veins is r
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are shifted to the right side of the developing cardiac septa, as the caval system replaces the primitive cardinal system of vessels, is of vital importance in understanding the functioning of the developing heart. The right-left imbalance in cardiac intake thus set up involves the necessity of compensatory shunting mechanisms (Patten, 1946). *On the intake side* we shall see the shunt in the form of the series of interatrial communications which are maintained throughout fetal life. *On the output side*, the shunt is effected by the ductus arteriosus which persists until after birth. It is only when one realizes that the maintenance of intracardiac balance is as important to the fetus as it is to the adult, and comprehends the mechanisms which effect the balancing, that the sequence of events in the partitioning of the heart can be logically interpreted.

The First Embryonic Blood Corpuscles. While the heart and the main vascular channels of the embryo have been taking shape, changes leading toward the formation of the first blood corpuscles of the embryo are occurring in the yolk-sac (Sabin, 1922; Bloom and Bartelmez, 1940). Connecting with the developing vitelline blood vessels in the splanchnopleure of the yolk sac are prevascular cords of mesodermal cells, as yet not hollowed out. In these cellular cords are frequent knotlike enlargements, known as *blood islands* (Figure II-14A), containing not only cells which are destined to form vascular endothelium but also cells which will give rise to blood corpuscles. In the differentiation

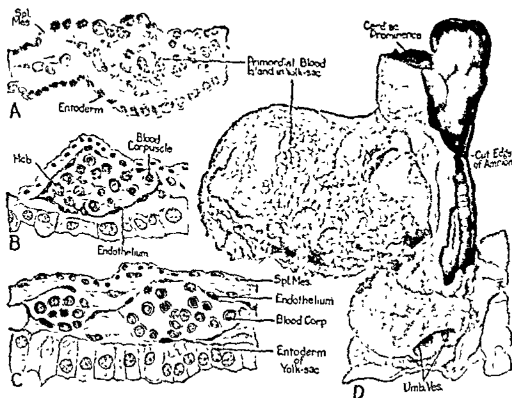


Figure II-14. Development of yolk-sac blood islands. A-C are camera lucida drawings, reproduced X 335. A. Early stage in aggregation of cells between entoderm and splanchnic mesoderm in yolk-sac of an embryo early in fourth week (17 somites). B. Beginning of differentiation of endothelium and primitive blood cells, from an embryo of about four weeks (4.5-mm.). C. A more advanced area from a four-week embryo showing endothelium well differentiated and corpuscles suspended free in plasma. D. The Corner 10-somite embryo showing location of young blood islands on yolk-sac. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

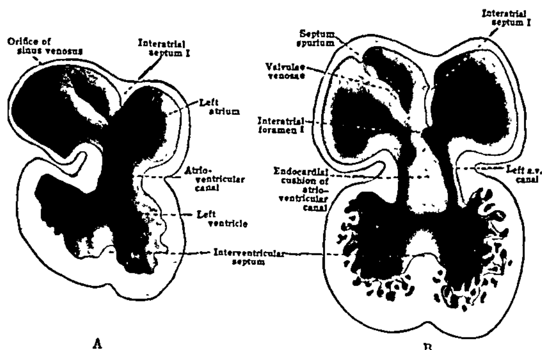


Figure II-16 Semischematic drawings of interior of heart to show initial steps in its partitioning A Cardiac septa are represented at stage reached in human embryos early in fifth week of development Note especially the primary relations of interatrial septum primum Based on original reconstructions of the heart of a 3.7-mm pig embryo, and on Tandler's reconstructions of corresponding stages of the human heart B Cardiac septa as they appear in human embryos of sixth week. Note restriction of interatrial foramen primum by growth of interatrial septum primum Based on original reconstructions of the heart of 6-mm pig embryo, on Born's reconstructions of rabbit heart, and Tandler's reconstructions of corresponding stages of the human heart (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

divided blood stream entering its sinoatrial end and being pumped out of its ventricular end

Partitioning of the Atrium and Atrioventricular Canal. The basis of the partitioning of the heart into right and left sides is largely laid down during the second month of development, but the final phases of this division and the rerouting of blood streams involved cannot be completed until after birth when the placenta ceases to be the source of oxygen and lung-breathing begins In the separation of the primitive common atrium into right and left chambers two septa are directly involved. These, on the basis of their sequential appearance, are commonly called septum primum and septum secundum (Born, 1889, Tandler, 1912, Odgers, 1938, Patten, 1946). Starting as a crescentic ridge on the dorsocephalic part of the atrial wall, *septum primum* grows toward the atrioventricular canal (Figure II-16).

At about the same time that septum primum is making its appearance, the first indications of the impending division of the original common atrioventricular canal into a right and a left channel become evident. Two local thickenings, one dorsally, the other ventrally located, appear in the walls of the canal These thickenings are the endocardial cushions of the atrioventricular canal. Each cushion consists of a plastic mass of embryonal connective tissue, of the type characteristically appearing in the developing heart at points where septa will fuse, or where elaborate connective-tissue structures such as the cardiac valves are destined to be molded. During the sixth week of development the dorsal

and ventral cushions are brought into contact with each other by their own growth, and fuse to form a common mass dividing the atrioventricular canal (Figures II-16 to II-18). *There is then left between the concave margin of septum primum and the growing atrioventricular canal cushions a progressively diminishing opening known as the interatrial foramen primum, or ostium primum* (Figures II-16B and II-18)

While these changes have been occurring, the sinus venosus has been shifted out of the midline so that it opens into the atrium to the right of the newly formed interatrial septum (Figure II-16). The heart is now in a critical stage of development. Its simple tubular form has been altered so that the four chambers characteristic of the adult heart are clearly recognizable. But there is as yet no division of the blood stream because there are still open communications from the right to the left side in both atrium and ventricle A little further progress in the growth of the partitions, however, and the two sides of the heart would be completely separated. Were this to occur in the young embryo, the left side of the heart would become almost literally dry. An insignificant amount of blood from the undeveloped lungs is all that would enter it, for the sinus venosus into which systemic, portal, and placental currents all enter has, as we have seen, come to open on the right of the interatrial septum The partitions in the ventricle and in the atrioventricular canal do progress rapidly to completion (Figures II-16, II-18 and II-19) but an interesting series of events takes place at the interatrial partition which assures that an adequate supply of blood will reach the left atrium and thence, the left ventricle.

Just when septum primum is about to fuse with the endocardial cushions of the atrioventricular canal, closing the inter-

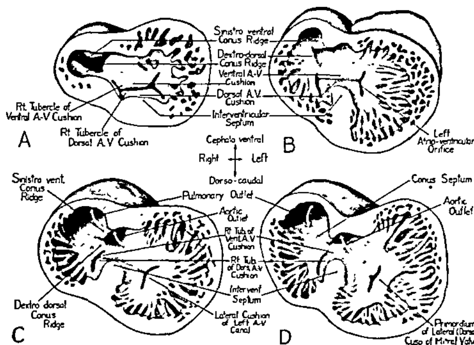


Figure II-17. Four stages in partitioning of atrioventricular canal (After Kramer, *Am J Anat*, Vol. 71, 1942) The apex of the ventricle has been cut off and the heart is viewed from below In this aspect, the relations of conus ridges to A-V canal cushions and to the upper part of interventricular septum are especially instructive.

are shifted to the right side of the developing cardiac septa, as the caval system replaces the primitive cardinal system of vessels, is of vital importance in understanding the functioning of the developing heart. The right-left imbalance in cardiac intake thus set up involves the necessity of compensatory shunting mechanisms (Patten, 1946) *On the intake side*, we shall see the shunt in the form of the series of interatrial communications which are maintained throughout fetal life. *On the output side*, the shunt is effected by the ductus arteriosus which persists until after birth. It is only when one realizes that the maintenance of intracardiac balance is as important to the fetus as it is to the adult, and comprehends the mechanisms which effect the balancing, that the sequence of events in the partitioning of the heart can be logically interpreted.

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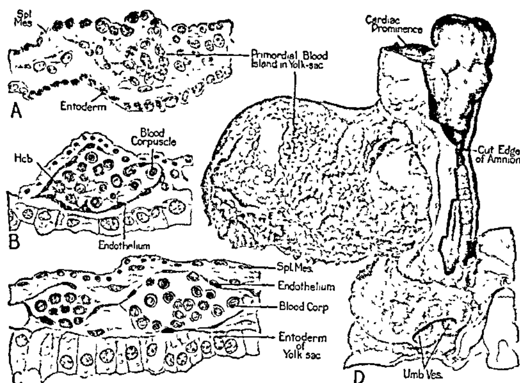


Figure II-14 Development of yolk-sac blood islands A-C are camera lucida drawings, reproduced X 355 A Early stage in aggregation of cells between entoderm and splanchnic mesoderm in yolk-sac of an embryo early in fourth week (17 somites) B Beginning of differentiation of endothelium and primitive blood cells, from an embryo of about four weeks (4 5-mm) C A more advanced area from a four-week embryo showing endothelium well differentiated and corpuscles suspended free in plasma D The Corner 10-somite embryo showing location of young blood islands on yolk-sac (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

circulation of blood has commenced. If the sequence of events in the human embryo is comparable to that in the chick, it would be four or five days after the heart showed its first twitching before it set the blood in motion, probably some time late in the third, or early in the fourth week of development.

THE CONVERSION OF THE PRIMITIVE TUBULAR HEART TO ITS DEFINITIVE CHAMBERED CONDITION

To appreciate the significance of the changes which occur in the growing heart, one must have in mind the exigencies under which it develops Starting as a simple tube, with the blood passing through it in an undivided stream, it must become converted into an elaborately valved, four-chambered organ, partitioned in the midline and pumping from its right side a pulmonary stream which is returned to the left side and pumped out again by way of the aorta as the systemic blood stream. And the heart cannot cease work for alteration; there can be no interruption in the current of blood it pumps to the growing embryo. This is but one phase of the matter. The pulmonary arc of the circulation cannot work up gradually to full functional activity because it is impossible for the lungs to take in air until after birth. Yet the pulmonary circulation must, at the moment of birth, be ready to take over the entire responsibility of oxygenating the blood. Furthermore, in the early phases of development the left side of the heart can receive but a small volume of blood from the lungs because no more can pass through them in their undeveloped condition. Yet it must be ready at the time of birth to pump through the myriad peripheral vessels of the systemic circulation the full blood stream received from the newly-functional lungs. These are some of the situations which must be faced before the heart can arrive at its adult condition. The manner in which they are met is doubly interesting because they seem at first sight so difficult.

One of the primary factors which lead toward the early regional differentiation of the heart is the rapid elongation of the primitive cardiac tube The heart increases in length so much faster than the chamber in which it lies that it is first bent to the side and then twisted into a loop Since the cephalic end of the heart is anchored in the body by the aortic roots, and the caudal end by the great veins, it is the midportion of the cardiac tube which, in the bending process, undergoes the most extensive changes in position. This is facilitated by the early disappearance of the dorsal mesocardium which leaves the heart entirely free in its midregion.

During the period in which the cardiac loop is being formed, the primary regional divisions of the heart have, as we have seen, become clearly differentiated (Figure II-8). Almost from their earliest appearance the atrium and the ventricle show external indications of the impending division of the heart into right and left sides. A distinct median furrow appears at the [illegible] II-8D [illegible] der- [illegible] on either side of the midline (Figures II-8 and II-29) Its bilobed configuration is emphasized by the manner in which the truncus arteriosus compresses it midventrally.

Thus by the end of the first month of development the principal regional divisions of the heart are recognizable Functionally, however, the heart is still acting as a simple contractile tube with an un-

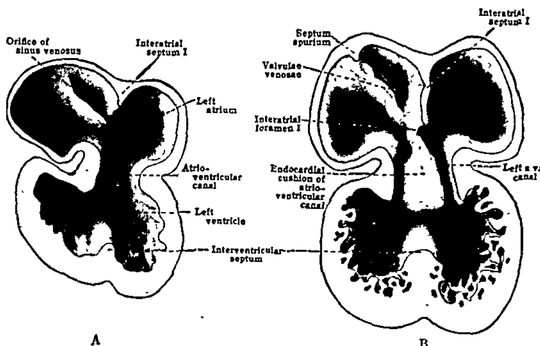


Figure II-16. Semischematic drawings of interior of heart to show initial steps in its partitioning A Cardiac septa are represented at stage reached in human embryos early in fifth week of development Note especially the primary relations of interatrial septum primum Based on original reconstructions of the heart of a 3 7-mm pig embryo, and on Tandler's reconstructions of corresponding stages of the human heart B Cardiac septa as they appear in human embryos of sixth week. Note restriction of interatrial foramen primum by growth of interatrial septum primum Based on original reconstructions of the heart of 6-mm pig embryo, on Born's reconstructions of rabbit heart, and Tandler's reconstructions of corresponding stages of the human heart (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

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At about the same time that septum *primum is making its appearance*, the first indications of the impending division of the original common atrioventricular canal into a right and a left channel become evident. Two local thickenings, one dorsally, the other ventrally located, appear in the walls of the canal. These thickenings are the endocardial cushions of the atrioventricular canal. Each cushion consists of a plastic mass of embryonal connective tissue, of the type characteristically appearing in the developing heart at points where septa will fuse, or where elaborate connective-tissue structures such as the cardiac valves are destined to be molded. During the sixth week of development the dorsal

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While these changes have been occurring, the sinus venosus has been shifted out of the midline so that it opens into the atrium to the right of the newly formed interatrial septum (Figure II-16) The *heart is now in a critical stage of development.* Its simple tubular form has been altered so that the four chambers characteristic of the adult heart are clearly recognizable. But there is as yet no division of the blood stream because there are still open communications from the right to the left side in both atrium and ventricle. A little further progress in the growth of the partitions, however, and the two sides of the heart would be completely separated. Were this to occur in the young embryo, the left side of the heart would become almost literally dry An insignificant amount of blood from the undeveloped *lungs is all that would enter it, for* the sinus venosus into which systemic, portal, and placental currents all enter has, as we have seen, come to open on the right of the interatrial septum. The partitions in the ventricle and in the atrioventricular canal do progress rapidly to completion (Figures II-16, II-18 and II-19) but *an interesting series of events takes place at* the interatrial partition which assures that an adequate supply of blood will reach the left atrium and thence, the left ventricle

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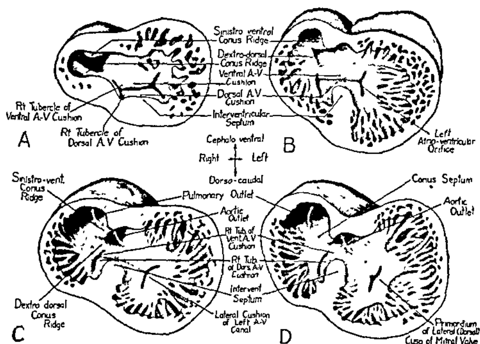


Figure II-17. Four stages in partitioning of atrioventricular canal (After Kramer, *Am J Anat*, Vol. 71, 1942) The apex of the ventricle has been cut off and the heart is viewed from below. In this aspect, the relations of conus ridges to A-V canal cushions and to the upper part of interventricular septum are especially instructive

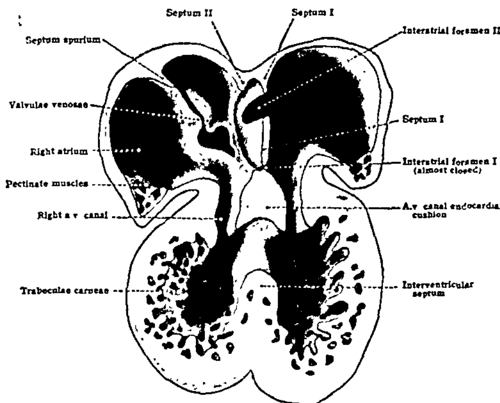


Figure II-18 Semischematic drawing of interior of heart to show start of interatrial septum secundum and appearance of interatrial foramen secundum in septum primum Based on original reconstructions of the heart of a 9 4-mm pig embryo and on Tandler's reconstructions of the heart of human embryos of seventh week. (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

atrial foramen primum, a new opening is established The more cephalic part of septum primum is resorbed * to form *interatrial foramen secundum.* The appearance of a second interatrial communication, just as the initial one is closing, is of fundamental significance because the constant presence of an interatrial communication makes it possible for the left atrium to receive, without interruption, a contribution from the blood entering the right atrium.

More than the atrial part of the heart is *involved in this matter of balanced atrial* intakes, for the atrioventricular canal is divided by the 10-mm. stage, and at about the 16- to 17-mm. stage the interventricular septum separates the right and left ventricles from each other. After these partitions are completed, if the atrial intakes were unbalanced the ventricular intakes would inevitably be correspondingly disturbed. That this is a matter of more than theoretical importance is clearly shown by the conspicuously defective development of the left side of the heart which is encountered when, as occasionally happens, abnormal development prematurely closes or markedly narrows the interatrial communication of the fetal heart (Patten, 1938, see also Figure V-9).

* Interatrial foramen secundum develops first in

independently without being incorporated into the main interatrial foramen secundum If such accessory openings are low in their location, they may appear in the fully formed heart in the part of septum primum which lies opposite the subsequently formed foramen ovale in *septum secundum* and serves as its valve (Figure II-44C and D). Such ectopic openings are particularly interesting from the theoretical standpoint in that they represent a developmental defect which is the result of excess resorption, instead of being in any sense a "developmental arrest."

About the time the secondary interatrial opening is formed in septum primum, another septum begins to develop. Like septum primum, *septum secundum* is crescentic in shape, but the open part of the crescent is directed more caudally and dorsally — toward the inferior part of the sinus inlet rather than toward the atrioventricular canal as was the case with septum primum The more cephalic tip of septum secundum lies along the cephalodorsal wall of the atrium (Figure II-18). The more caudal tip merges with the endocardial cushions of the atrioventricular canal just to the right of the line of fusion formed by interatrial septum primum in the closure of primary interatrial communication (Figure II-28D). There is, as development progresses, a consolidation of interatrial septum primum and septum secundum to form that part of the definitive interatrial septum which fuses with the partition dividing the atrioventricular canal (Figures II-28E and F). There is, moreover, some interdependence in the growth of these septa at this point. If the atrioventricular cushions fail to fuse, interatrial septum primum will tend to remain undeveloped on the atrial side of this defect If the canal cushions and septum primum are defective, septum secundum follows their lead and fails to grow into the characteristically shaped opening in the interatrial septum just above the point where it should have fused with the partition of the atrioventricular canal. Such a defect (Figures V-1*a* and *b*) is usually spoken of as a persistent interatrial foramen primum although this designation does not take adequate account of a possible underlying factor in defective growth of the atrioventricular canal cushions, nor of the secondary deficiency in the growth of the caudal limb of septum secundum which seems to follow if septum primum has not laid the basis for its extension

As septum secundum grows, its concave margin for a time cuts progressively farther into the atrial lumen; but septum secundum is not destined to become a complete partition. Its extension gradually ceases, leaving a characteristic oval aperture which is the *foramen ovale* (Figures II-19 and II-28) The margin of septum secundum thus constitutes what in adult anatomy is called the *limbus* or *annulus fossae ovalis.*

The relations of septum primum to the oval foramen persisting in septum secundum are of vital importance The secondary opening in septum primum is formed so near the cephalic wall of the atrium that the unresorbed lower part of septum primum lies as a loose flap, covering on its left atrial side the oval opening in septum secundum (Figure II-19) In this position it acts as a one-way valve, permitting the filling of the left atrium from the right but effectively shutting off return flow In the fully formed fetal heart this flap is commonly known as the *valvula foraminis ovalis* rather than by its embryologic name, septum primum

Primary Muscular Part of the Interventricular Septum. Indications of the division of the primitive ventricle into right and left chambers appear at about the same time that the first interatrial septum becomes recognizable. Early in the second month the primary muscular part of the *interventricular septum* appears at the apex of the ventricular bend, leaving an *interventricular foramen* between its crescentic margin and the bottom of the partition in the atrioventricular canal (Figure II-16)

In its earliest stages the interventricular septum appears to be little more than a ridge of trabeculae carneae (Streeter, 1948). When it is carefully reconstructed a fine flexible probe can be passed through it from one ventricle to the other by way of the intertrabecular spaces As deve[illegible] ment progresses the trabeculae tend

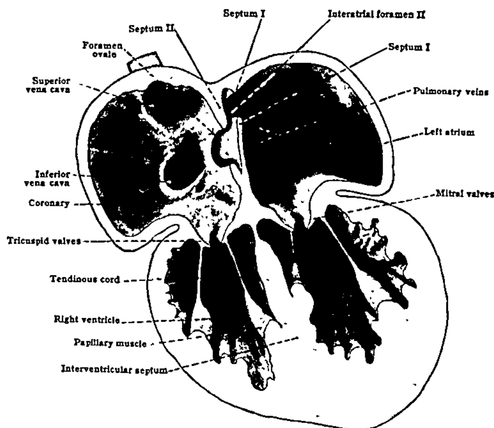


Figure II-19 Schematic drawing to show interrelations of septum primum and septum secundum during latter part of fetal life Note especially the way in which the lower part of septum primum is situated so that it acts as a one-way valve at the oval foramen in septum secundum (From Patten, *Human Embryology,* courtesy of The Blakiston Company)

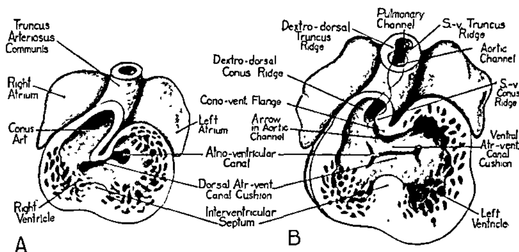


Figure II-20. Semischematic dissections of developing heart viewed in frontal aspect to show relations of importance in establishing aortic and pulmonary outlets (After Kramer, *Am J Anat*, Vol 71, 1942)

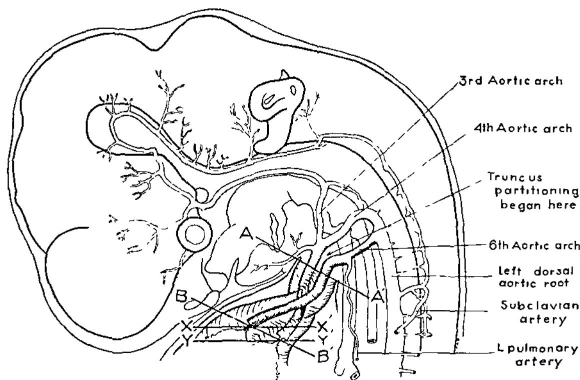


Figure II-21 Diagram showing the spiral course of the truncoconal partitioning, based on conditions in embryos of about 14-mm (early in seventh week) The line A-A' indicates the level of the sections diagrammed in Figure II-22, the line B-B' indicates the level of the sections diagrammed in Figure II-23, the lines X-X' and Y-Y' indicate the locations of the photomicrographs appearing as Figure II-24, A and B

come more compactly arranged to form a relatively solid myocardial mass Occasionally, however, this consolidation may not be complete, with the resultant persistence of small tortuous interventricular openings in the main muscular portion of the septum.

The interventricular septum is usually described as growing toward the atrioventricular canal cushions and thus progressively reducing the size of the interventricular foramen This serves well enough to emphasize the relative changes seen in comparing hearts of different ages (Figures II-16 and II-18); but it expresses in somewhat oversimplified terms what has actually happened. Actually it would be more nearly correct to say that the ventricular chambers on either side of the septum expand, leaving the septum projecting relatively farther into the enlarged ventricular lumen and causing the interventricular foramen to appear smaller in comparison with the size of the septum The interventricular foramen, instead of having its closure delayed until after birth as is the case in the atrium, is closed surprisingly early Normally all traces of the opening will have disappeared by the end of the second month (embryos of 17 to 19 mm) The final closure of the interventricular foramen is not, however, accomplished by the main muscular part of the septum. The last remaining opening is closed by a composite mass of connective tissue derived in part from the connective-tissue margin of the interventricular septum itself, in part from the base of the endocardial cushions forming the partition in the atrioventricular canal, and in part from the conus ridges.

Partitioning of the Truncus Arteriosus and Formation of the Aortic and Pulmonary Valves. The involvement of the conus

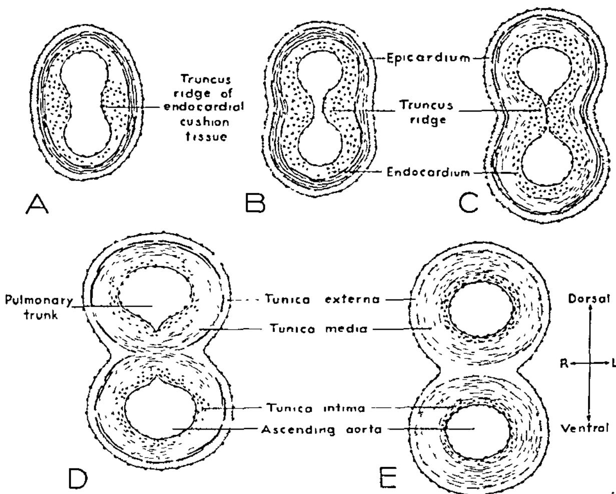


Figure II-22. Schematic diagrams showing the partitioning of the truncus arteriosus to form the ascending aorta and the pulmonary trunk The relations are depicted as they would appear at the level of the line A-A' in Figure II-21

ridges in the closure of the interventricular foramen makes it necessary to take up at this point the partitioning of the truncus arteriosus, for the conus ridges are merely prolongations into the ventricle of the ridges which fuse to divide the truncus into aortic and pulmonary channels. The partitioning of the truncus begins distally between the roots of the fourth and sixth aortic arches and continues back through the truncus toward the ventricles. The division is effected by the growth of a pair of ridges composed of the same type of plastic young connective tissue which we saw constituting the atrioventricular canal cushions (Frazer, 1917; Spitzer, 1919-21, 1922; Odgers, 1938; Kramer, 1942). As these ridges grow, they cut more and more deeply into the lumen of the truncus (Figure II-22A and B) and finally meet to form a complete partition (Figure II-22C and E), separating an aortic channel leading into the fourth aortic arches and a pulmonary channel leading into the sixth aortic arches (Figure II-21). The fact that these truncus ridges pursue a spiral course as they grow toward the ventricles accounts for the way the ascending aorta and the main pulmonary trunk twist around each other as they emerge from the ventricles (Figure III-1). The same spiraling brings the aortic channel around into a position to receive the blood pumped by the left ventricle, and the pulmonary channel into

a position to receive the right ventricular output (Figures II-20B, II-21 and II-26)

The level at which the *aortic and pulmonary valves* develop may be regarded as the line of demarcation between the truncus arteriosus and the tapering ventricular outlet called the conus Here, there is a local elaboration of the endocardial cushion tissue of the truncus ridges In the walls of both the aorta and the pulmonary trunk three small pads of plastic young connective tissue develop and bulge into the lumen (Figures II-23D and E and II-24B). The two pads in either vessel which lie adjacent to the point of fusion of the ridges appear to develop as local enlargements of the ridge tissue. The primordia of the dorsal valve of the aorta and of the ventral valve of the pulmonary trunk are formed by independent local growth centers in the intima opposite the points of fusion of the ridges. For this reason, the primordia of these cusps have been aptly described by Kramer (1942) as the dorsal and ventral *intercalated valve swellings* (Figure II-23C). Gradually each of these buttonlike masses of intimal connective tissue becomes molded into one of the cusps of the semilunar valves of the aorta or of the pulmonary artery. During the later stages of development there is further rotation of the aorta and the pulmonary trunk about each other so that the aortic valve cusp which arose from the dorsal intercalated valve swelling is carried around into a dextral position, and the pulmonary valve cusp which arose from the ventral intercalated cushion is carried into a sinistral position (cf Figure II-23E with Figure II-27)

Closing of the Interventricular Foramen and Attainment of Definitive Relations at the Ventricular Outlets. On the ventricular side of the aortic and pulmonary valves ridges of the same type which appeared in the truncus are continued into the funnel-

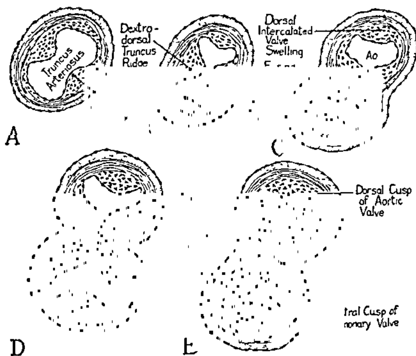


Figure II-23 Schematic cross-sectional diagrams to explain partitioning of truncus arteriosus The relations are depicted as they would appear at the level of the developing semilunar valves (line B-B' in Figure II-21). (After Kramer, *Am J Anat*, Vol. 71, 1942)

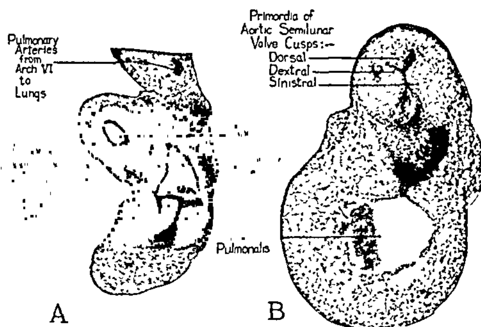


Figure II-24 Photomicrographs of sections through developing aortic and pulmonary valves of a 13-mm human embryo (After Kramer, *Am J Anat*, Vol 71, 1942)

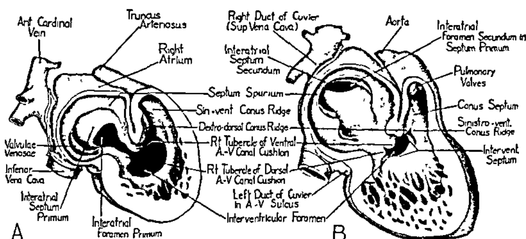


Figure II-25 Schematic lateral dissections to show relations of various septa in the developing heart. (Kramer-Patten From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

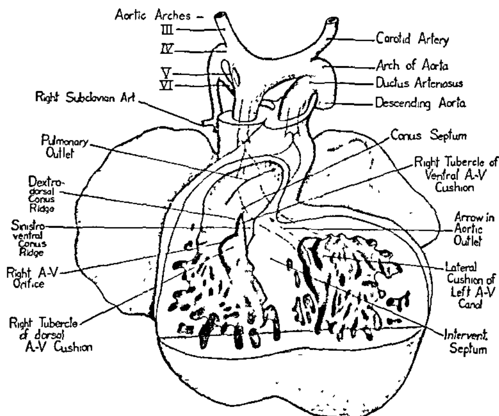


Figure II-26 Reconstruction of heart of a 13-mm embryo, opened to show relations of conus septa to interventricular septum and the atrioventricular canal cushions (After Kramer, *Am J Anat*, Vol 71, 1942)

shaped *ventricular outlet under the name* of the *conus ridges* (Figures II-20B and II-26). These conus ridges follow a direct continuation of the spiral course of the truncus ridges The rate of turn of the spiral is such that it brings the conus ridges in line with the crest of the interventricular *septum and reduces, from above, the* size of the interventricular foramen (Figure II-25). Local enlargements (tubercles) of the right margin of the endocardial cushions of the atrioventricular canals also crowd into the diminishing interventricular foramen (Figures II-17 and II-26) Thus the *final* closure of the *interventricular* foramen is accomplished, not by the growth of the primary crescentic muscular septum, but by a plastic mass of connective tissues derived mostly from the conus ridges and from the right tubercles of the *atrioventricular canal cushions*, with a small contribution from the connective tissue that caps the crest of the muscular part of the interventricular septum This composite mass of connective tissue completing the interventricular septum is at first rather bulky and loosely organized (*Figure II-28E*). *As the septal cusps* of the atrioventricular valves are molded, and as the connective tissue itself becomes more highly differentiated, the interventricular septum at this point of final closure gradually becomes a thin fibrous sheet (Figure II-28F), known as the *membranous part of the interventricular septum (pars membranacea septi)*

When one reviews mentally all the various developmental processes involved in the partitioning of the ventricles and the division of the truncus arteriosus into aor-

tic and pulmonary trunks, it does not seem surprising that the region of the ventricular outlets is one of the commonest sites of developmental disturbances. It is not enough that each component part, such as the truncus septum, must be laid down according to a certain pattern. Other components, such as the main muscular part of the interventricular septum and the atrioventricular canal cushions, starting elsewhere in the growing heart, must also follow their appointed course and attain the appropriate degree of development in order to be joined, one with the other, at just the right place. Moreover, all the component parts must meet, not only at the right place, but also at the right time; for if one is unduly delayed, the associated parts will develop beyond their early condition of plasticity which makes possible the necessary fusions. This matter of the "*timing*" *of developmental processes* is, incidentally, one of the most easily overlooked, yet most vitally important, of the factors underlying malformations, and one concerning which we need much more precise information than we possess at present.

The developmental malformations of the heart are to be dealt with in detail in Chapter V. It is not, therefore, pertinent here to do more than call attention to the special vulnerability of this particular region and the general way in which some of the growth processes here being considered may be disturbed. For example, unequal division of the truncus arteriosus as a result of malplaced truncus ridges may produce an unduly narrow pulmonary trunk with a correspondingly overlarge aorta. Conversely, if the malposition of the truncus ridges is in the reverse direction, one is confronted with an aortic stenosis and a large pulmonary trunk. In both such cases, the conal prolongation of the truncus septum tends also to be out of position. It is not surprising, therefore, that when one of its component primordia is disturbed the septum membranaceum is likely to remain incomplete. Such a correlated sequence of events is what presumably underlies "the large aorta arising astride of an interventricular septal defect" which is such a characteristic part of the picture in the so-called tetralogy of Fallot.

The foregoing examples merely suggest the kind of developmental disturbances which involve the relations of the aortic and pulmonary outlets of the ventricles. A recent extensive and exceedingly valuable study by Shaner (1949) emphasizes the manner in which early maldevelopment of the endocardial cushions of the atrioventricular canal may be an underlying cause in malformations of the truncus region. The frequency with which these and related malformations are encountered make it particularly important to be thoroughly *familiar with the normal development and* topography of this region of the heart.

The accompanying diagrams (Figure II-27), showing the normal relations of the aortic and pulmonary outlets, were drawn from the unconventional but very effective approach used in some of Taussig's (1947) illustrations portraying the conditions in pulmonary stenosis. The locations of the aortic and pulmonary outlets are projected on a cross section of the underlying ventricle in such a manner that their relations to the septum membranaceum are especially emphasized. In A, which represents schematically the relations in fetal hearts, it will be seen that the aortic outlet is not rotated as far around behind the pulmonary outlet as is usually the case in adult hearts. It should, however, be noted that in adult hearts there is considerable individual variation in these relations and any configuration between the characteristic fetal and adult relations here diagrammed *should probably be regarded as within* normal limits. Another point of interest brought out by these diagrams is the fact,

often overlooked, that the right and left ventricular walls of the fetal heart are of approximately equal thickness. The marked preponderance of the left ventricular wall in adult hearts is a postnatal characteristic acquired gradually during the first three or four years of life (Gross, 1921).

In following the sequence of events in the partitioning of the heart, consideration of many other concurrent developmental changes was postponed for the sake of coherence. It is now, therefore, necessary to take up such subjects as the manner in which the atrioventricular valves are formed; the changes which occurred in the sinus venosus while the atrium and ventricle were being subdivided, the way nerves and vessels reach the growing heart, and something of the origin of the sinoventricular conduction system

Atrioventricular Valves and Papillary Muscles. At the point where the right and left atrioventricular canals open into the ventricles there are early indications of the establishment of valves. From the partition which divided the originally single atrioventricular canal, and from the outer walls on each side, masses of tissue in the shape of thick, blunt flaps project toward the ventricle (Figure II-18). It is these masses of a primitive type of connective tissue similar to that in the endocardial cushions of the canal which later become differentiated into the flaps of the adult atrioventricular valves The processes involved are gradual alterations in shape, accompanied by slow histogenetic modifications of the character of the component tissues Changes of this type do not lend themselves readily to description by ages or stages, and we must seek rather to grasp their major trends.

One of the essential features of any cardiac valve is the *fibrous annulus* to which its leaflets are attached and which reinforces the orifice against overdilation as the pressure builds up behind closed valves At first the undivided atrioventricular orifice of the young embryonic heart is encircled by tissue which is almost entirely developing cardiac muscle There is only a

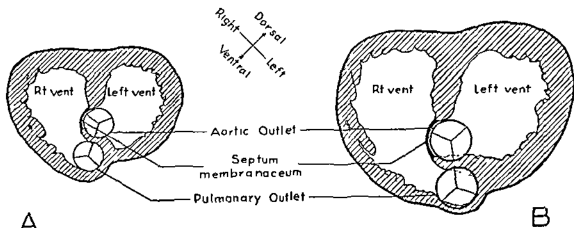


Figure II-27 Diagrams to show the relations of the aortic and pulmonary outlets to the membranous portion of the interventricular septum The outlets and their semilunar valves are projected onto a schematized cross section of the underlying ventricles in a manner suggested by some of Taussig's illustrations A. Fetal relations when right and left ventricular walls are of equal thickness B. Relations as seen in a child of four years or older, when the left ventricular wall has attained its adult degree of preponderance and there has been some further rotational change in the positions of the aortic and pulmonary outlets. Note that the diagrams are oriented on the basis of the division of the heart into right and left sides by the interventricular septum, as one might hold the excised heart in his hand For the position of the heart in the body, turn the page so the arr representing the dorsoventral axis is vertic

very thin outer epicardial layer, consisting of little more than mesothelium, and an endothelial layer which is just beginning to be backed by a scanty amount of connective tissue that has not yet progressed to the stage of fiber formation (Figure II-28A and B). When the atrioventricular canal is divided into right and left channels by the fusion of endocardial cushion masses (Figure II-28C and D), the foundation is laid for the mesial portion of each of the atrioventricular rings. Concurrently, the epicardial connective tissue begins to cut into the myocardium at the atrioventricular sulcus By the end of the eighth week (Figure II-28E), it has met the endocardial tissue so that all around the atrioventricular constriction the myocardium of the ventricle is cut off from the myocardium of the atrium by connective tissue. There remain, connecting atrial and ventricular myocardium, only slender fascicles of young cardiac muscle fibers which extend from the floor of the right atrium into the dorsal limb of the crescentic muscular part of the interventricular septum and thence along its crest There they bifurcate to send fibers into each ventricular wall. This persisting group of myocardial fibers is destined to be differentiated into the atrioventricular bundle (bundle of His) and its main branches. These will receive further consideration when the sinoventricular conduction system, of which they are a part, is discussed.

The same connective tissue growth which tends to separate atrial from ventricular muscle establishes the primordium of the so-called cardiac skeleton Around each of the now separate atrioventricular orifices the plastic young connective tissue begins to differentiate the circularly disposed collagenous fiber bundles that form the tricuspid and the mitral annuli. Toward the lumen similar young connective tissue is molded into flange-like projections which constitute the primordia of the atrioventricular valves (Figure II-28D). From the way in which we have seen the two atrioventricular canal cushions fuse with each other to divide the atrioventricular canal, it is evident that the primordial tissue for the septal leaf of the tricuspid valve and for the medial leaf of the mitral valve must arise, in part, from the dorsal and, in part, from the ventral endocardial cushion of the atrioventricular canal. This is a point of importance in understanding the notching of these valves which is so generally seen in connection with defects low down in the atrial septum (Figure V-4). In such instances of persistence of interatrial foramen primum there is apparently a coexisting tendency for the atrioventricular canal cushions to lag somewhat in their growth and fusion, and it is this tendency which leaves its record in the form of the characteristic notching of the valves.

As the flanges which constitute the valve primordia become extended, the trabeculated myocardium is carried out on their ventricular surfaces. For a time, therefore, the developing valve has loosely organized young connective tissue continuous with the trabeculae of the heart wall on its ventricular face (Figure II-28E). In the final molding of the valves, the muscle on their ventricular face undergoes retraction and regression, so that the basis of the valve flaps becomes entirely connective tissue At the same time, the muscle pulls away from the part of the trabeculae directly adherent to the valve and thus leaves only slender fibrous strands which are the forerunners of the *tendinous cords* (Figure II-28F). The basal portions of these same trabeculae thereby become relatively thickened to constitute the *papillary muscles.*

The latest phases of valve development involve the histologic maturing of its component parts. In the annulus are developed heavy interlacing bundles of collagenous fibers which constitute the valve ring and at the same time send out strands which

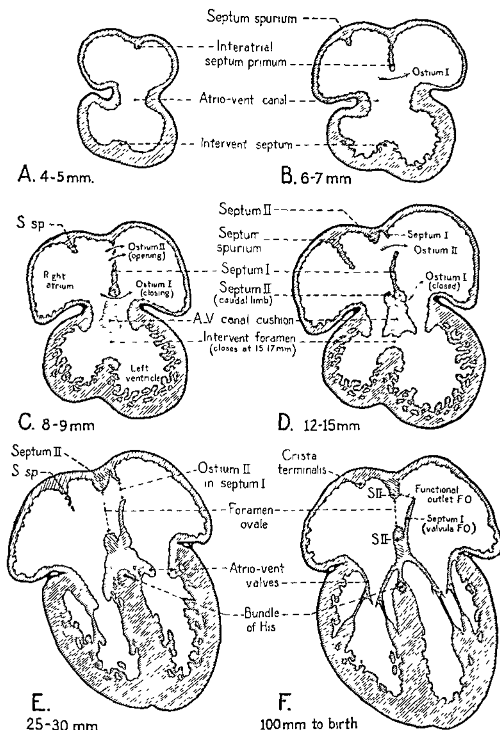


Figure II-28 Sectional plans of embryonic heart in frontal plane, showing extent of growth *of various cardiac septa at several stages of development* These diagrams give specifically for the human embryo a more precise picture of the rate of progress of partitioning than do the preceding schematic drawings Stippled areas in the diagrams indicate distribution of endocardial cushion-tissue, muscle is shown in diagonal hatching, and epicardium in solid black [illegible]
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anchor the base of the valve leaflets to the annulus. The tendinous cords come to be constituted by parallel bundles of collagenous fibers anchored in perimysial tissue of the papillary muscles. Last of all to make its appearance is the strongly developed meshwork of slender elastic fibers which are so characteristically interlaced with the finer collagenous bundles of the atrial faces of the adult valves. In the light of the retraction of the myocardium from its early association with the valve primordium, the occasional presence of a few rudimentary muscle fibers in the subendothelial connective tissue of the valvular endocardium is readily understandable. The curious ill-defined histologic picture these fibers often present in the adult has led to their being confused with the smooth muscle cells that occur sporadically in the endocardial tissue in many places in the heart Under favorable conditions, however, the cardiac character of these rudimentary muscle elements of the ventricular surface of the atrioventricular valves can be clearly seen Throughout all the changes we have been considering, the endothelium at all times constitutes an unbroken covering of the developing valves themselves and their associated tendinous cords and papillary muscles.

Changes in the Sinus Region. The so-called sinus venosus of the embryonic heart has not been as carefully studied as it merits. Moreover, the fact that the composition of the sinus venosus is so radically different at various ages has led to considerable looseness in its description. In early stages, what is commonly called the sinus venosus is merely the region of confluence of the great veins which bring the blood back to the caudal end of the primitive tubular heart (Figure II-29C). The sinus venosus as it appears in somewhat older hearts is still essentially the region of confluence of the entering veins, but additional mesial fusion of the primary omphalomesenteric vessels has occurred so that the original sinus territory has been increased, and the opening into it of the newly formed caval inlet further changes its configuration (Figure II-29D). Concurrently, the epimyocardium comes to invest the sinus endocardium more and more completely (Figure II-29C-E) At the same time, also, the opening of the sinus into the atrium is shifted out of the midline so that it comes to lie on the right side of the developing interatrial septum (Figure II-16). These changes, taken in conjunction with the rapid expansion of the atrium, in increasingly intimate association with which the sinus develops, soon combine to give the sinus somewhat the shape of a lopsided "U" bulging out on the dorsal wall of the atrium (Figure II-29D). The limbs of the "U," into which the right and left common cardinal veins enter, are usually spoken of as the "horns of the sinus."

The early U-shaped condition of the sinus does not long persist With the formation of the left innominate vein as a new transverse anastomosis between the right and left anterior cardinals (Figure II-12D), more and more blood is shunted to the right so that the right common cardinal progressively increases in size, a change indicative of its conversion into the superior vena cava (Figure II-29E and F) At the same time the left common cardinal, toward the heart from the anastomosis, becomes correspondingly smaller. Where it crosses the dorsal wall of the left atrium, if it persists in a reduced state into adult life, it is known as the *oblique vein of the left atrium* or *vein of Marshall* (Figure II-29F). As the blood from its original cephalic drainage area is reduced, the most proximal part of the left common cardinal which lies across the dorsal wall of the heart in the atrioventricular sulcus begins to acquire new tributaries from the heart itself. When this has occurred we may well

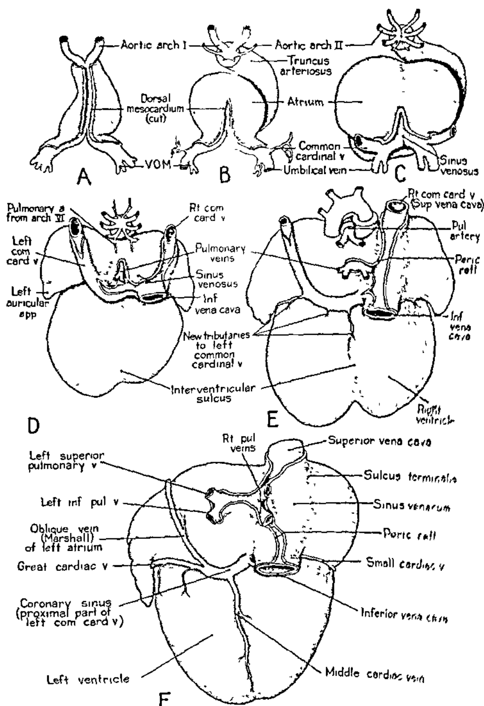


Figure II-29 Six stages in the development of the heart, drawn in dorsal aspect to show changing relations of sinus venosus and great veins entering heart A. Two and one-half weeks (8-10 somites) B Three weeks (12-14 somites). C Three and one-half weeks (17-19 somites). D Five weeks (6-8 mm, C-R) E. Eighth week (embryos about 25-mm.) F. 11 weeks (embryos of about 60-mm.) (From Patten, *Human Embryology*, courtesy of The Blakiston Company.)

call it by its adult name, *coronary sinus* (Figure II-29E and F). The original left horn of the sinus venosus, in this process, becomes greatly reduced in relative size and what remains of it merges with the proximal part of the left common cardinal vein in the formation of the coronary sinus (Figure II-29F).

While the right common cardinal vein has thus been relatively increased by the innominate shunt to form the superior vena cava, the inferior cava has increased even more strikingly in size. The rerouting of systemic (Figure II-12) and portal and placental venous returns (Figure II-13) through the liver to converge in the inferior vena cava is, as we have seen, the underlying reason for this relatively tremendous growth. The inevitable result of the increase in blood volume returning through the two venae cavae is the marked relative enlargement of the original right horn of the sinus venosus to form, in the adult heart, the *sinus venarum* (Figure II-29F)

As both the right horn of the sinus venosus and the right atrium grow in size, the external boundaries between the two regions become progressively less conspicuous Mesially the border of sinus territory comes to merge with the external depression opposite the interatrial septa; on the right a shallow groove, known as the *sulcus terminalis*, marks its boundaries. The extent to which the old boundaries become thus inconspicuous has led to the not-too-accurate statement that "the sinus venosus is absorbed into the dorsal wall of the right atrium."

Internally, in young hearts, the opening of the sinus venosus into the right atrium is flanked by a pair of well developed valves, the *valvulae venosae* (Figure II-16). At the cephalic end of the sinus orifice the two valves merge into a flange-like structure which projects deep into the right atrium from its dorso-cephalic wall. This structure is known as the *septum spurium* because, although it is very prominent in the hearts of two- to three-month-old fetuses, it later undergoes regression without playing any part in the partitioning of the right and left atrial chambers Its reduction is accomplished by a resorptive process starting simultaneously in many areas, so that when it is partially reduced it is likely to have almost a lace-like appearance. The anomalous meshwork of strands sometimes found in adult hearts attached along the crista terminalis and the margins of the eustachian and thebesian valves, named "Chiari's net" (Figure V-10A and B), represents vestiges of the right valvula venosa and its continuation as the septum spurium, which have persisted when the process of resorption by which they are normally molded has remained incomplete.

Concurrently with the blending of the right sinus horn into the dorsal wall of the right atrium externally, there are even more striking changes internally. The progressive resorption of the valvulae venosae and the septum spurium and the partial incorporation of the sinus into the expanding right atrium gradually result in the superior and inferior cavae and the coronary sinus all opening independently. The reduced septum spurium is now represented only by the crista terminalis and the much reduced remains of the right venous valve are converted into the highly variable *eustachian valve* of the inferior vena cava and *thebesian valve* of the coronary sinus The frequency with which small perforations appear in both these valves is indicative of the nature of the resorptive process by which the redundant young valvulae venosae are, so to speak, "cut down to size."

Although not usually conspicuous, lace-like remnants of the lower part of the reduced left venous valve will occasionally be seen in adult hearts lying closely ad-

herent to septum II near the caval inlet and sometimes extending across the limbus fossae ovalis to adhere to the valvula foraminis ovalis (Figure V-10C).

The Coronary Circulation. The origin of the main coronary veins has been considered in connection with the formation of the coronary sinus into which they drain The coronary arteries arise from the aorta during the seventh week, shortly after it has been partitioned off in the division of the truncus arteriosus. Careful study of serial sections is necessary to identify the newly formed coronary arteries for they are very small when they first appear in embryos of 14 to 15 mm. (crown rump length), and their delicate endothelial lining is easily missed in the loose young connective tissue above the primordial valve pads which they traverse in their origin. Once established, the coronary arteries enlarge quite rapidly and it is not difficult to trace their course (Figure II-30). The right coronary emerges from the aorta to traverse the groove between the pulmonary conus of the right ventricle and the right auricular appendage, and then courses along the coronary sulcus to the diaphragmatic surface of the heart, giving off at intervals branches which enter the myocardium The left coronary artery emerges between the base of the pulmonary trunk and the left auricular appendage to send its main branch along the interventricular sulcus and give off a smaller, circumflex branch in the left atrioventricular sulcus.

The smaller branches of the coronary arteries, when they enter the myocardium, break up into an extraordinarily rich bed of capillaries investing the developing muscle fibers. Most of the blood entering this plexus is returned by way of the coronary veins. Some of the small vessels, however, make connection with the endothelially-lined spaces among the trabeculae In young hearts, these *intertrabecular spaces* are relatively large. As the trabeculae become more robust the spaces are greatly reduced so that, in the deeper parts of the myocardium, they come to be of about the order of magnitude of sinusoids. When this has occurred, it becomes virtually impossible, in sections, to tell which small endothelially-lined space was derived from the ingrowth of sprouts from the invading coronary vessels, and which was derived by reduction of the original intertrabecular spaces. The so-called *venae minimae cordis*, the orifices of which can be found to open at many places into the cardiac cavities, really represent reduced intertrabecular spaces communicating with the maze of endothelially-lined crevices of similar origin which, in turn, receive blood from connections with the coronary circulation Only by a realization of the nature of this unorthodox vascular relationship can one acquire an understanding of some of the abnormalities encountered in the coronary circulation Particularly is this the case in communications such as those sometimes seen in an aberrant coronary (or coronary branch) which enlarges one of its primary connections, with the intertrabecular spaces of one of the ventricles, usually the right. Sizable channels of this type have been misdescribed as "aneurysms" originating in an aortic sinus and extending through the myocardium to emerge in the pulmonary cone of the right ventricle

The Nerves to the Heart. From the functional standpoint the details of the nerve supply of even the adult heart are still inadequately known Its double innervation from sympathetic and parasympathetic sources is, of course, quite familiar, together with the antagonistic accelerator and depressor effects of these two sets of nerves on heart rate. But as they approach the heart, sympathetic and parasympathetic fibers become intricately

mixed in the so-called cardiac plexus, and the terminal distribution of fibers within the heart itself and their precise functions still offer challenging problems. Even less satisfactory is our knowledge of the embryologic development of these two categories of nerves supplying the heart. We do, however, have some basic information as a starting point (Streeter, 1912, Shaner, 1930). The parasympathetic fibers from the vagus are easier to follow in early stages than are the sympathetic fibers. The primordial ganglionic cell cluster of the vagus becomes recognizable as a vaguely defined mass of neuroblasts of neural crest origin early in the fourth week. In the fifth week the jugular ganglion and the nodose ganglion with its component of neuroblasts of epibranchial origin are clearly recognizable. By the sixth week, growing motor nerve fibers from neuroblasts within the brain stem, and sensory fibers from neuroblasts in the ganglia have extended to form a strongly developed visceral branch of the vagus nerve following along each side of the trachea and esophagus. Among these growing nerve fibers are many cells, some of which are destined to be neurilemma-sheath cells; others, which are neuroblasts migrating along the developing nerve, are destined to form ultimately the terminal ganglion cells that give rise to the second-order neurons of the two-neuron parasympathetic efferent chain. At cardiac level, delicate branches turn off and follow along the developing aortic and pulmonary trunks toward the main mass of the heart. In these branches, also, are many migrating neuroblasts along with the growing nerve fibers. By the seventh week the main vagal branches to the developing cardiac plexus are clearly recognizable (Figure II-31).

The preganglionic sympathetic fibers concerned in relaying impulses to the postganglionic fibers which enter the cardiac plexus arise from cell bodies, most of which are located in the first four thoracic segments of the spinal cord. Some arise in the fifth thoracic segment and possibly a few also in the sixth. These fibers enter the ganglia of the prevertebral sympathetic chain and pass cephalad to one of the cervical, or to the first thoracic ganglion. There they synapse with the second-order (postganglionic) neurons, the fibers of which constitute the cardiac nerves. The neuroblasts from which these postganglionic fibers are formed have come into the chain ganglia from the spinal ganglia at corresponding levels. These cells travel along the developing spinal nerve and the ramus communicans to aggregate in their characteristic prevertebral locations. It is probable that they are joined by other neuroblasts which arise in the mantle layer of the developing spinal cord and migrate out along the ventral nerve roots, so that the cells from both sources move together along the course of the ramus communicans. The ganglia of the sympathetic chain which originate in this manner do not make their appearance as early as the ganglia of the vagus nerve, but by the seventh week they are readily recognizable and the postganglionic fibers arising from their neuroblasts

← Figure II-30. Photomicrographs showing early steps in the establishing of the coronary arteries. A. Section of heart of 14.8-mm embryo passing through the aortic outlet. (Photo X 35 from EH 314.) B. Section of aortic outlet of 19-mm embryo. (Photo X 60 from EH 358.) The plane of cutting is unusually fortunate in showing both coronary orifices in the same section. C. Section of aortic outlet and part of wall of left ventricle of 31.5-mm. embryo. (X 60 from EH 377.)

(All embryos from the University of Michigan Embryological Collection. The collaboration of Richard Licata in the preparation of this illustration is [illegible])

artery; SV, primordial semilunar valves of aorta.

have begun to mingle with the vagus fibers extending to the heart (Figure II-31). Thus, before the end of the second month it is possible to recognize quite clearly both the sympathetic and parasympathetic components of the cardiac plexus

It is quite probable that better technical methods will permit us to recognize migrating neuroblasts moving into the cardiac region somewhat earlier than they have been demonstrated by the studies at present available It seems unlikely, however, that even the well-organized fibrocellular strands, which we can readily recognize as developing nerves by our present routine staining methods, have as yet begun to function in the transmission of impulses. It is highly significant that, in forms which can be secured for study under experimental conditions, the pulsation of the heart has commenced and the blood has been effectively set in motion in the embryonic circulation, long before even the first neuroblasts from the vagus can be seen moving out toward the territory in which they later take part in the formation of the cardiac plexus. This

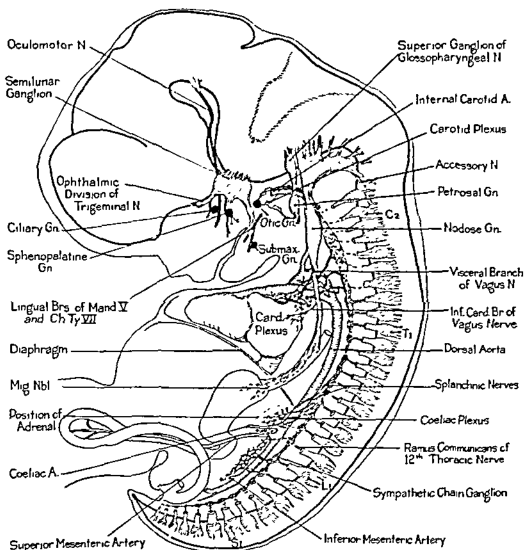


Figure II-31. The autonomic nervous system of a human embryo (16-mm.) of the seventh week. (From Patten, *Human Embryology*, redrawn after Streeter, courtesy of The Blakiston Co)

fact, taken in conjunction with the autonomous rhythm maintained by excised embryonic hearts, *leaves no room to doubt* the primary myogenic character of the embryonic heart beat. We would seem *fully justified in concluding that when the* nerves grow in and make connections with the heart that is already beating, their *effect is limited to a secondarily* superimposed regulation of its rate of pulsation

The Sinoventricular Conduction System. Some of the experimental work which has been done on the initiation of the beat and its propagation in young embryonic hearts (Patten and Kramer, 1933, Armstrong, 1935; Goss, 1938, 1940, 1942, Copenhaver, 1945) provides the best possible basis for understanding the so-called sinoventricular conduction system of the adult heart. In discussing the formation of the primary tubular embryonic heart, emphasis was laid on the fact that the various regions were formed in cephalocaudal sequence, as the closing of the foregut permitted the paired cardiac primordia to meet in the midline. Thus the first part of the heart to be formed is the conoventricular portion. This is followed by the formation of the atrium and, last of all, by the establishing of the sinus venosus

Contractile activity begins to involve the cardiac regions in the same sequence in which they are formed. The first contractions appear in the conoventricular myocardium, before fusion of the paired primordia is completed in the atrium, and while the sinus venosus is represented only by endocardial primordia which are still widely separated from each other and which are entirely devoid of myocardial covering The initial rate of pulsation in the primitive ventricle is relatively slow When fusion of the cardiac primordia has extended caudad to establish the atrium and this part of the cardiac tube begins to pulsate, the rate for the entire heart is increased. Transecting the beating heart clearly demonstrates which part of the heart is dominant in the control of its rate (*Patten and Kramer, 1933; Paff, 1936*). In such experiments the isolated atrium continues to beat at essentially the rate exhibited by the entire heart before it was cut. The isolated ventricular part drops down to a much slower rate, approximating that characteristic for the early phases of development when the ventricle was the only part of the heart beating. Similar cutting experiments carried out at a later stage, after fusion of the cardiac primordia has established the sinus venosus caudal to the atrium, show that sinus myocardium has a faster rate than atrial myocardium The picture presented by three isolated segments, cut from the same tubular heart, each beating at its own characteristic rate, is most dramatic It means that there is a gradient in the contraction rate of the myocardial primordia, with the intrinsic rate of pulsation becoming progressively higher as the myocardial samples are excised from the more and more caudal parts of the cardiac tube During development, then, there is not "a" pacemaker in the heart but rather a succession of pacemaking zones, with new areas added behind the already established ones showing a progressively faster inherent rhythm and assuming, in turn, domination of the slower beating regions previously laid down. Thus the slower rate of beating of the ventricle is accelerated when faster-beating atrial tissue is added behind it, setting the pace for atrioventricular contraction waves. When, a little later, the still-faster-beating sinus venosus is added behind the atrium, it assumes the pacemaking function and sino-atrio-ventricular contraction waves are established. In this manner, as the cardiac tube itself differentiates, it is traversed by peristaltoid contraction waves initiated in what is, at the moment, its most caudal part. Since this most caudal pa[illegible]

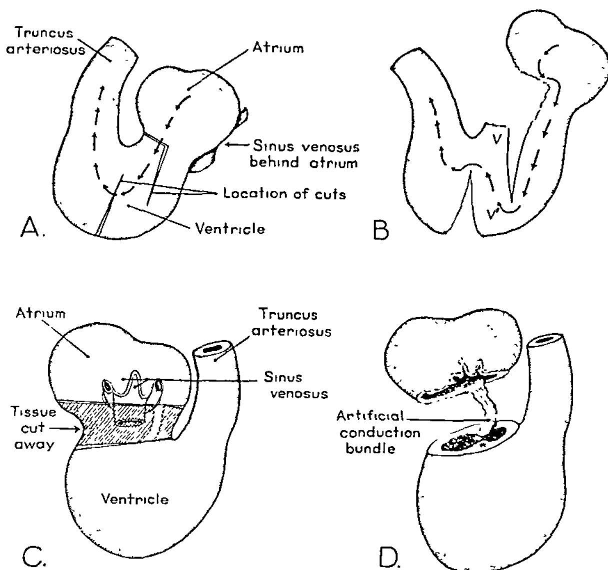


Figure II-32. Cutting experiments illustrating the conductive properties of embryonic cardiac muscle. The excised hearts were kept alive at body temperature in oxygenated Locke-Lewis solution for study and micro-moving picture recording of their action before and after experimental incisions

A. Ventral view of heart removed from three and one-half day chick embryo The arrows show the general direction in which the wave of contraction traversed the heart before the cuts were made

B Same heart diagrammed in A after making cuts in the locations there indicated Note especially that the placing of the cuts is such that in the part of the ventricle V-V' the beat is propagated in practically the reverse of its normal direction.

C. Dorsal view of heart removed from four-day chick

D Four-day heart with "artificial conduction bundle" made by cutting away the tissue in the regions indicated by diagonal hatching in C. Note that the artificial bundle was made by leaving a strand of muscle in the ventral part of the heart wall in a region as far as possible from that in which the His bundle later appears The asterisk on the cut surface indicates the region where the His bundle would have been differentiated at a considerably later period of development

same time the blood-receiving end of the heart, it would be difficult to postulate a more simple and efficient means of propelling blood through a pump that is still valveless.

By zig-zag cutting experiments, it is possible to demonstrate that the entire embryonic myocardium at these early stages is effective in propagating the beat from the faster to the slower beating parts of the heart. Moreover, it is even possible, by carefully-planned placing of interdigitating cuts, to make the impulses travel through muscle areas in a radically different direction from that which they normally traverse (Figure II-32). Such experiments vividly emphasize the conductive capacity of embryonic cardiac muscle and make it seem only natural that certain retained tracts of it come to serve as the *path of propagation of beats in adult* hearts. In this connection it is interesting to note that by employing adequate amplification it is possible to secure electrocardiographic records from embryonic hearts still in the primitive tubular stage (Hoff, Kramer, DuBois and Patten, 1939) These tracings change progressively in character as the cardiac tube is lengthened. Well before the sinoventricular conduction system has been histologically differentiated the embryonic myocardium yields polyphasic tracings essentially similar to those characteristic of the adult heart

The details of the steps by which the sinoventricular conduction system is differentiated are far from adequately known Certain of the major points, however, seem reasonably clear (Shaner, 1929). In discussing the formation of the fibrous rings of the atrioventricular orifices, attention was called to the fact that originally the atrial myocardium and the ventricular myocardium are broadly continuous throughout the entire circumference of the atrioventricular constriction (Figure II-28A through C) Gradually the *epicardial and endocardial connective tissues* encroach on the myocardium at the atrioventricular sulcus and ultimately interrupt the broad connection between atrial and ventricular muscle (Figure II-28D through F). The separation is rapidly completed peripherally around the sulcus, but there persists a connecting fascicle of muscle *fibers from the dorsomedial part of the floor* of the right atrium (Figure III-24), penetrating the fibrous base of the heart (Figure III-19) and extending along the crest of the primary muscular portion of the interventricular septum (Figure III-22). This is the *atrioventricular bundle (bundle of His)* Like the young cardiac muscle from which it arises, it retains its capacity for transmitting the impulse to contract and it ultimately becomes one of the critically *important parts of the sinoventricular* conduction system of the adult heart.

Traced into the ventricular myocardium the main atrioventricular bundle bifurcates and sends branches, the *right and left bundle branches* (Figures III-25 and III-26), along the septal walls of the two ventricles These branches recurve in the lateral walls of ventricles and break up into richly branching strands of atypical cardiac muscle, *(the Purkinje fibers)* (Figure III-27) which lie close beneath the ventricular endocardium. If one recalls the way the ventricles of the embryonic heart grow, in effect ballooning out on either side of the interventricular septum, it should be evident that the atrioventricular bundle, its right and left branches and their ramifications can be thought of as representing a sort of primary core of embryonic cardiac muscle. The bundle is all that remains of the original extensive connection between atrium and ventricle, and the branches and their terminal ramifications are, so to speak, dragged out along the lines *of expansion of the ventricular chambers* As will be brought out in the next chapter

(Chapter III) all the parts of the sinoventricular conduction system are essentially cardiac muscle, although each part of the system has its own peculiar histologic characteristics

The remaining parts of the sinoventricular conduction system are the *sinoatrial* and *atrioventricular nodes.* In the adult heart the sinoatrial node lies in the shallow sulcus where the inferior vena cava enters the right atrium (Figure III-24) In the formation of this region a considerable portion of the right horn of the sinus venosus has been incorporated in the dorsal wall of the right atrium, so that the sinoatrial node represents myocardium which was originally associated with the sinus horn This is the most caudal part of the myocardial primordium and, in accordance with the cephalocaudal gradient in contraction rate, it is the most rapidly pulsating. It is therefore quite logical that, once it has been established, we should find it retaining its dominance over the contraction rate of the heart as a whole and becoming its adult pacemaking center.

The steps in the formation of the atrioventricular node are less well known and can be outlined only tentatively on the basis of present information It seems probable, however, that it should be regarded as starting its development as the counterpart on the left sinus horn, of the sinoatrial node on the right. Young embryonic hearts appear to have for a time bilaterally symmetrical pacemaking areas located, one on either side, where the common cardinal veins enter the horns of the sinus venosus. Some adult reptilian hearts, moreover, appear to have retained this condition of paired sinus pacemakers It will be recalled that with the shifting of the sinus venosus to the right, the left common cardinal is pulled far to the right (Figure II-29D and E). Thus, myocardial tissue originally lying at the junction of the left common cardinal vein wit the left sinus horn could well be carrie along with the positional changes involve in the conversion of left common cardin and left sinus horn into the coronary sinu The adult location of the atrioventricula node in the floor of the right atrium clos to the inlet of the coronary sinus (Figur III-25) is entirely in keeping with th tentative interpretation of its develop mental history This concept of the tw nodes as originally symmetrical structure may also make it easier to understand wh all the many careful attempts to trac connections from the sinoatrial to the atrio ventricular node have so far proved un successful. Just how the contractile im pulse passes from the sinoatrial to atrio ventricular nodes, and how the sinoatria node came to take over the dominant rol in the pacemaking function from its orig inal partner, are some of the most challeng ing unsolved problems in basic cardia physiology at the present time.

Pericardial Relations. The pericardial pleural, and peritoneal cavities of th adult develop as subdivisions of the coelom of the embryo. The embryonic coelomi cavities are primarily paired, arising o each side of the midline by splitting o the lateral plate of mesoderm into an oute (somatic) layer and an inner (splanchnic) layer, with the coelom between. The par of the coelom which is destined to be seg regated as the pericardial cavity appear very early in development (Figures II-1 and II-2) At the time the cardiac primordia take shape the original paired condition of the coelom in the pericardial region still persists (Figure II-3A and B). As the young tubular heart is molded, the splanchnic mesodermal layers which form its epimyocardium meet in the midventral line to complete the investment of the endocardial primordia Where they come in contact with each other beneath the heart, they immediately break through so

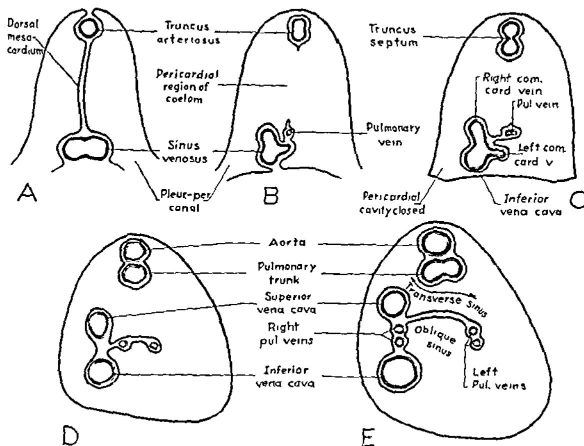


Figure II-33 Schematic diagrams showing a series of stages in the [illegible] cavity from which the heart has been removed The orifices outlined in red are the arterial outlets, those outlined in blue are venous inlets The heavy black lines represent the cut pericardial reflections about the vessels and peripherally, the cut parietal pericardium These figures should be carefully compared with the dorsal views of a series of removed hearts showing comparable stages (Figure II-29)

that the originally separate right and left coelomic chambers become confluent ventral to the heart (Figure II-3C). For a time the newly established tubular heart is suspended beneath the pharynx by a double layer of splanchnic mesoderm, known as the dorsal mesocardium, which continues to separate the original coelomic chambers dorsally (Figures II-3C and D and II-33A) As the cardiac tube lengthens and begins to bend (Figure II-4), the dorsal mesocardium breaks through and leaves the heart suspended by its two ends in the pericardial portion of the coelom. Caudally the pericardial chamber still communicates on either side with the rest of the coelom (Figure II-7) by way of the pleuropericardial canals (Figure II-33A and B). With the closure of these canals the pericardial chamber is established as an isolated cavity (Figure II-33C through E).

In the light of the foregoing events it should be apparent that the outermost layer of the heart has remained directly continuous with the lining of the pericardial chamber at two points: (1) where the truncus arteriosus is attached beneath the pharynx and (2) where the sinus venosus is suspended by a persisting part of the dorsal mesocardium at the caudal end of the pericardial chamber (Figures II-7 and

II-33B and C). In other words, it is at these two areas that the *epicardium (visceral pericardium)* is continuous with the *parietal pericardium.* The changes which take place as development progresses beyond this basic condition are the obvious ones entailed by the division of the truncus into aorta and pulmonary trunk, and by increase in the number of separate venous orifices as the sinus venosus is incorporated into the dorsal wall of the right atrium and the pulmonary veins are formed.

The changes which occur at the truncus are so simple that they call for no comment The changes in the pericardial reflections at the sinus end of the heart can best be understood by comparing the diagrammatic plots of Figure II-33 with the dorsal views of removed hearts drawn to show the development of the sinus venosus (Figure II-29) In these drawings the cut edges of the pericardium are shown where they were reflected from the parietal walls of the pericardial cavity to become the epicardial (visceral pericardial) layer of the heart In Figure II-33 the heavy black lines about the appropriately colored vascular orifices represent the same reflections as they would appear on the dorsal wall of the pericardial cavity from which the heart has been removed. As the sinus venosus is incorporated into the growing right atrium, the originally single orifice (Figure II-33A) is replaced by separate orifices for the superior and inferior venae cavae (Figure II-33B through D). At the same time the left common cardinal vein (future coronary sinus) acquires its own opening into the heart (Figure II-33C) and the fold of mesocardium which surrounded it at early stages (Figure II-29D) disappears, as the coronary sinus becomes closely applied to the heart wall (Figure II-29E and F).

While these changes have been going on in the main vessels entering the sinus venosus, the *pulmonary veins* have been taking shape. The primary venous plexus which is organized in connection with the growing lung-buds originally drains into channels which connect with the anterior cardinal veins. Gradually, however, there is developed a new medial collecting channel that enters the atrial region dorsally. This channel, at first a single median vein collecting blood by a tributary vein from each lung, reaches the left atrium by passing between the reflected pericardial layers which represent persisting portions of the dorsal mesocardium (Figures II-29D and II-33B) As the heart grows, the single median portion of the pulmonary venous channels appears to be incorporated into the atrial wall so that its main right and left tributaries come to empty by two separate orifices (Figures II-29E and II-33C) As the right and left orifices become progressively more widely separated from each other the mesocardial fold enclosing them is pulled out transversely (Figure II-33C and D). Ultimately this process of eliminating the proximal portions of the pulmonary veins continues until it involves the first main bifurcation on the right and on the left, so that there come to be two right and two left pulmonary vein orifices (Figure II-33E).

The changes in the manner of entrance of the pulmonary veins just considered leave a transversely placed reflection of the pericardium with a caudal extension on the left enclosing the two left pulmonary veins, and a longer caudal extension on the right enclosing the two right pulmonary veins and the inferior vena cava The bay-like pericardial space so bounded is known as the *oblique sinus* (Figures II-33E and III-6) Concurrently the *transverse sinus* is being delimited. When the midportion of the dorsal mesocardium is resorbed, the two sides of the pericardial cavity are placed in open communication dorsal to the heart (Figures II-7 and 33B). This communication is the transverse sinus in

primordial form. As development progresses, the cardiac tube is bent into a tight loop and its receiving and discharging ends are brought relatively closer together. In this process the original pericardial communication dorsal to the heart is narrowed and its caudal boundary is remolded by the changes which we have just been following in the sinus region (Figures II-29 and II-33). These changes, however, merely alter the detailed configuration of the transverse sinus and in no way change its original essential relations as a communication from one side of the pericardial cavity to the other, dorsal to the heart. It is of course this relationship which places it in sharp contrast with the oblique sinus which is essentially a bay, or pocket, ending blindly behind the heart (Figures II-33E and III-6).

THE CHANGES IN CIRCULATION FOLLOWING BIRTH

All the steps in the partitioning of the embryonic heart lead gradually toward the final adult condition in which the heart is completely divided into right and left sides. Yet from the nature of its living conditions it is not possible for the fetus *in utero* fully to attain the adult type of circulation. The plan of the completely divided circulation is predicated on lung-breathing. In the adult the right side of the heart receives the blood returning from a circuit of the body and pumps it to the lungs where it is relieved of carbon dioxide and acquires a fresh supply of oxygen. The left side of the heart receives the blood that has just passed through the lungs and pumps it again through ramifying channels to all the tissues of the body. In the fetus the function of respiration is carried out in the placenta by interchange with the maternal blood circulating through the uterus. The lungs, although they are fully formed and ready to function in the last two months of fetal life, cannot actually begin their work until after birth. The radical change which must inevitably take place immediately following birth in the manner in which the blood is oxygenated has led to a widespread belief that there must be revolutionary changes in the routing of blood through the cardiovascular system. However, as the embryology of the circulatory system has been studied more closely from a functional angle, it is becoming increasingly clear that the heart and the great vessels develop in such a manner that the pumping load on the different parts of the heart remains balanced at all times during fetal life. Moreover, the very mechanisms which maintain this cardiac balance during intra-uterine life are perfectly adapted to rebalance the circulatory load on the new postnatal basis without involving any sudden overloading of previously inactive parts of the vascular system.

Course and Balance of Blood Flow in the Fetal Heart. To understand the changes in circulation which are so smoothly accomplished at the time of birth it is necessary to have clearly in mind the manner in which the way for them has been prepared during intra-uterine life. In the foregoing account of the development of the interatrial septal complex, emphasis was laid upon the fact that at no time were the atria completely separated from each other. It will be recalled that there is a succession of three morphologically distinct interatrial communications: the first, inferior to septum primum; the second, in septum primum; and the final one, in septum secundum. This permits the left atrium, throughout prenatal life, to receive a contribution of blood from the inferior cava and the right atrium by a transseptal

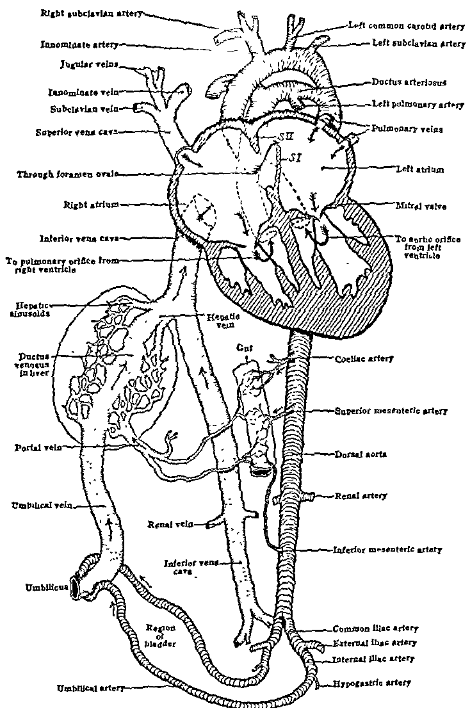


Figure II-34 Diagrammatic plan of fetal circulation just before birth (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

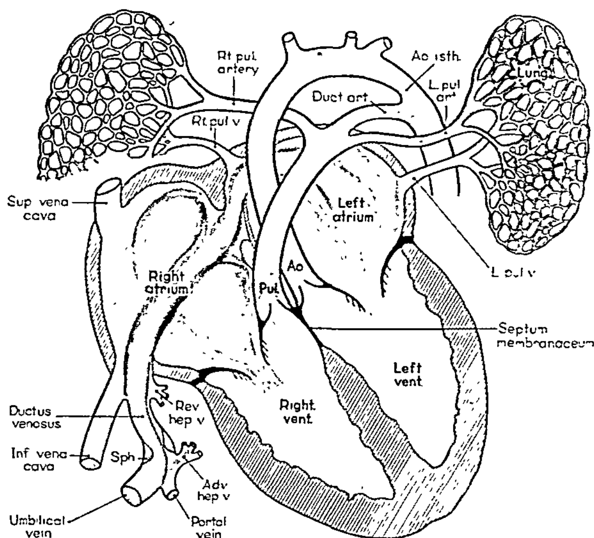


Figure II-35 Schematic diagram showing course of blood through fetal heart just prior to birth The colors symbolize relative degree of oxygen saturation
Abbreviations Ao. isth., aortic isthmus; Adv. hep v, advehent hepatic vein, Duct art., ductus arteriosus, Rev hep v., revehent hepatic vein, Sph., sphincter. When this sphincter is closed, blood from the umbilical vein is forced to pass through the sinusoidal channels of the liver, rather than taking the direct route through the ductus venosus

has now been supported by experimental work (Abel and Windle, 1939, Windle and Becker, 1940). A large prenatal pulmonary circulation of course means that, even in periods when a strongly flowing umbilical current minimized the admixture of portal blood and blood returning from the systemic circuit, there is still a considerable admixture in the left atrium of oxygen-depleted blood entering from the pulmonary circuit.

From the standpoint of smooth postnatal circulatory readjustments, the larger the pulmonary return becomes during fetal life, the less will be the balancing trans-atrial flow, and the less will be the change entailed by the assumption of lung-breathing. Very early in development, before the lungs have been formed, the pulmonary return is negligible and the flow from the right atrium through the interatrial ostium primum constitutes virtually the entire intake of the left atrium. After the ostium primum is closed and while the lungs

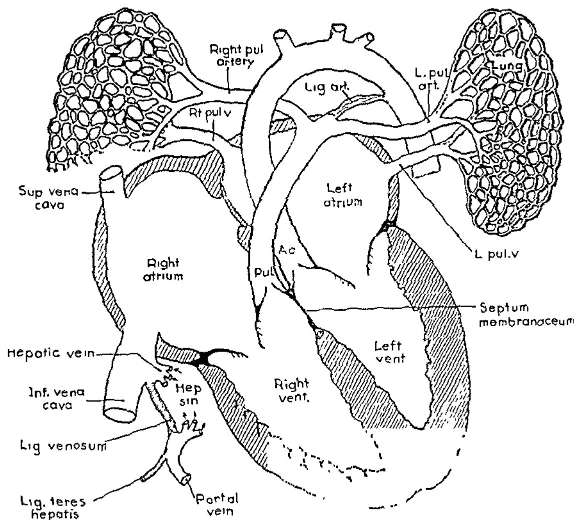


Figure II-36 Diagrams showing schematically the changes occurring in circulation at time of birth (From Patten, *Human Embryology*, courtesy of The Blakiston Company)

are but little developed, flow through the interatrial ostium secundum must still be the major part of the blood entering the left atrium. During the latter part of fetal life the foramen ovale in septum secundum becomes the transseptal route. As the lungs grow and the pulmonary circulation increases in volume, a progressively smaller proportion of the left atrial intake comes by way of the foramen ovale and a progressively larger amount is derived from the vessels of the growing lungs.

The balanced atrial intake thus maintained implies a balanced ventricular intake, and this in turn implies a balanced ventricular output We have seen, not in the heart itself but in the closely associated great vessels, a mechanism which affords an adequate outlet from the right ventricle during the period when the pulmonary circuit is developing. When the pulmonary arteries are formed from the sixth pair of aortic arches, the right sixth arch soon loses its original connection with the dorsal aorta. On the left, however, a portion of the sixth arch persists as a large vessel connecting the pulmonary artery with the dorsal aorta (Figures II-9, II-10 and II-34). This vessel, already familiar to us as the ductus arteriosus, remains open throughout fetal life and acts as a shunt, carrying over to the aorta whatever excess of

blood the vascular bed of the lungs at any particular phase of its development is not prepared to receive from the right ventricle. As has already been pointed out, the ductus arteriosus can be called the "exercising channel" of the right ventricle because it makes it possible for the right ventricle to carry its full share of work throughout development and thus be prepared for pumping all the blood through the lungs at the time of birth.

Postnatal Circulatory Changes. The two most obvious changes which occur in the circulation at the time of birth are the abrupt cutting off of the placental blood stream and the immediate assumption by the pulmonary circulation of the function of oxygenating blood (Figure II-36). One of the most impressive things in embryology is the perfect preparedness for this event which has been built into the very architecture of the circulatory system during its development. The shunt at the ductus arteriosus which has been one of the factors in balancing ventricular loads throughout development, and the valvular mechanism at the foramen ovale, which has at the same time been balancing atrial intakes, are perfectly adapted to effect the postnatal rebalancing of the circulation The closure of the ductus arteriosus is the primary event and the closure of the foramen ovale follows as a logical sequel. It has long been known that the lumen of the ductus arteriosus is gradually occluded postnatally by an overgrowth of its intimal tissue (Schaeffer, 1914; Scammon and Norris, 1918; Melka, 1926; Jager and Wollenman, 1942). This process in the wall of the ductus is as characteristic and regular a feature of the development of the circulatory system as the formation of the cardiac septa. Its earliest phases begin to be recognizable in the fetus as the time of birth approaches, and postnatally the process continues at an accelerated rate to terminate in complete anatomic occlusion of the lumen of the ductus about six to eight weeks after birth. Barclay, Franklin and Prichard (1944) have conducted a series of experiments, on animals delivered by cesarean section, which indicate that the ductus arteriosus closes functionally far sooner than it does anatomically. Following birth there appears to be a contraction of the circularly disposed smooth muscle in its wall which promptly reduces the flow of blood through the ductus. This reduction in the shunt from the pulmonary circuit to the aorta, acting together with the newly assumed respiratory activity of the lungs themselves, aids in raising the

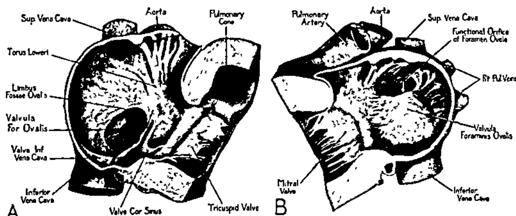


Figure II-37. Interior views of scale model of the human heart at term A Right atrial aspect showing foramen ovale. B Left atrial aspect showing outlet (functional orifice) of foramen ovale into left atrium Note that the valvula foraminis ovalis is bound sufficiently close to the septum so that the functional orifice is considerably smaller than the oval opening in septum secundum. (After Patten, Sommerfield and Paff, *Anat Rec.*, Vol 44, 1929.)

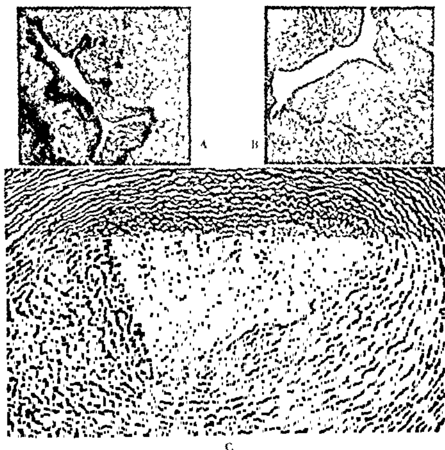


Figure II-38. Histologic changes involved in closure of ductus arteriosus A From an infant 21 days after birth Note padlike thickenings of intima B Infant 30 days [illegible] compared with A is probably [illegible] perimeter, [illegible] markedly [illegible] recently- [illegible] important [illegible] occludes [illegible] courtesy of W B Saunders Company)

pulmonary circulation to full functional level. At the same time the functional closure of the ductus by muscular contraction paves the way for the ultimate anatomic obliteration of its lumen by overgrowth of intimal connective tissue (Figure II-38). This concept of the immediate functional closure of the ductus is so appealing on theoretical grounds that a little extra caution in evaluating the evidence is indicated. It should be borne in mind that an initial tendency on the part of the circular smooth muscle of the ductus to contract does not necessarily imply a contraction sufficiently strong and steadily maintained to shut off all blood flow during the six to eight weeks occupied by morphologic closure (Kennedy and Clark, 1941) The dramatic quality of an immediate muscular response should not cause us to forget the importance of the slower but more positive structural closure.

The closure of the ductus arteriosus entails a gradual, although none the less striking, change in the configuration of the aortic arch (Patten, 1930; Noback and Rehman, 1941). Before birth there is a definitely narrowed portion of the arch be-

tween the point where the left subclavian is given off and the point of entrance of the ductus arteriosus. This narrowed region is called the *isthmus* (Figure II-39A). After the ductus arteriosus has been closed, all the blood entering the descending aorta must traverse the aortic arch and, as a result, the isthmus is slowly enlarged It is usually three to four months after birth before all trace of the narrowing which was so characteristic of the arch of the fetal aorta has entirely disappeared (Figure II-39B)

The results of increased pulmonary circulation with the concomitant increase in the direct intake of the left atrium are manifested secondarily at the foramen ovale Even before birth — in the latter part of fetal life, as the lungs attain considerable development — we have seen the beginning of reduction in transseptal flow. Following birth, as the pulmonary return increases still more, compensatory blood flow from the right atrium to the left decreases correspondingly, and finally ceases altogether This is indicated anatomically by a progressive reduction in the looseness of the valvula foraminis ovalis and the consequent diminution of the interatrial communication to a progressively narrower slit between the valvula and the septum (Figure II-40). When equalization of atrial intakes has occurred, the compensating one-way valve at the foramen ovale falls into disuse. Although, for several months after birth, a probe can still be passed freely behind the valvula, the foramen ovale may be regarded as functionally closed when this new intracardiac balance has been attained.

Then follows a period of six to eight months in which the connective tissue of the valvula increases from 600 to 700 per cent (Figure II-42). This second phase in the closure of the foramen ovale with its characteristic histologic alteration is essentially the conversion of an originally movable, flaplike valve into a fixed septal structure (Patten, 1931). Finally, coming leisurely in the wake of functional abandonment and as a culmination of the period of connective-tissue proliferation, is the adhesion of the valvula to become an integral part of the interatrial septum. There is great variability in the age at which this final step in the closure of the foramen ovale occurs. A usual range, rather than a specific time, of final anatomic closure is all that can be stated Substantiated cases of the fibrous adhesion of the valvula to the septum becoming complete under three months are exceed-

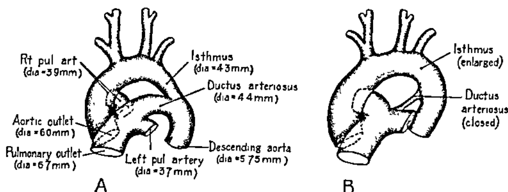


Figure II-39 Diagrams showing characteristic postnatal changes in isthmic region of aortic arch A Fetal condition at full term The vessel diameters are averages from the measurements of the internal diameters in 30 hearts B Typical configuration three to four months after birth Note enlargement of isthmic portion of the aortic arch which accompanies reduction of ductus arteriosus (Slightly modified from Patten, *Am Heart J.*, Vol 6, 1930)

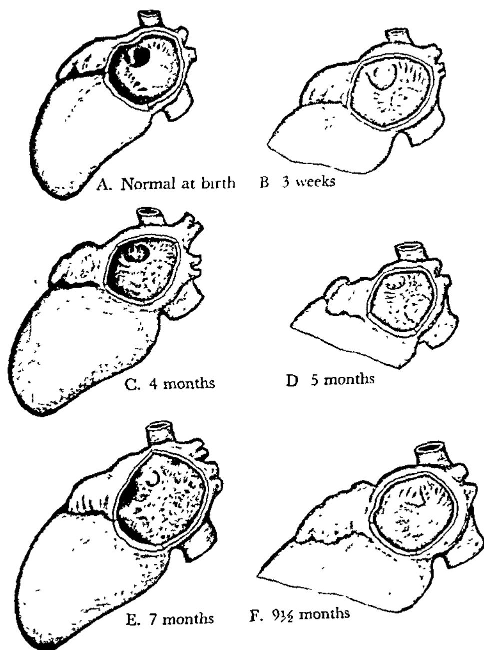


Figure II-40 Drawings of hearts with left atrium opened to show gross changes in valvula during period of closure of foramen ovale. Compare with Figure II-41, showing the microscopic changes. (From Patten, *Am J Anat.*, Vol 48, 1931)

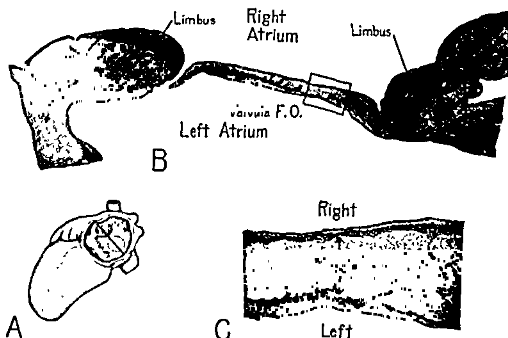


Figure II-41. Structure and relations of valvula foraminis ovalis at time of birth. A Orienting-sketch with left atrium opened. Heavy black line indicates location of section shown in B. B Photomicrograph of a section passing through interatrial septum at foramen ovale C More highly magnified photomicrograph of section through valvula at point indicated by rectangle on B (From Patten, *Am. J Anat.*, Vol 48, 1931.)

ingly rare. The usual time of complete anatomic closure appears to be not earlier than the last third of the first year after birth, and frequently it is much later.

In 20 to 25 per cent of persons the fibrous adhesion of the valvula to the septum is never entirely completed (Figure II-43). Provided the valvula amply overlaps the foramen ovale, such failures of complete adhesion appear to be no functional handicap to otherwise normal persons. The condition is best described as *probe-patency* (Patten, 1931, p. 40) in distinction to *open foramen ovale with incompetent valve* (cf. Figures II-43 and II-44). Because of the frequency with which they occur, probe-patencies may well be regarded as variations of the normal rather than as abnormalities. Such an attitude, however, must be tempered by the realization that in the event of disturbances in the pulmonary circuit sufficiently severe to unbalance intra-atrial pressures, an area of incomplete adhesion may again become a path for transseptal flow (see Chapter V, page 278).

Quite different from cases of nonadherence of the valvula with mere probe-patency are those in which the valvula is actually incompetent to close the foramen ovale (Figure II-44). Such a condition may be caused by abnormally extensive resorption of septum primum in connection with the formation of ostium secundum, or by insufficient growth of septum secundum leaving an abnormally large foramen ovale, or by a combination of both of these conditions (Patten, 1938). The functional implications of such interatrial defects will be discussed in Chapter V.

Even in the cases in which complete fibrous adhesion has occurred, the fetal valvular mechanism at the foramen ovale leaves its imprint on the anatomy of the adult heart. The sharply marked margin of the fossa ovalis records the former boundaries of the foramen ovale in septum

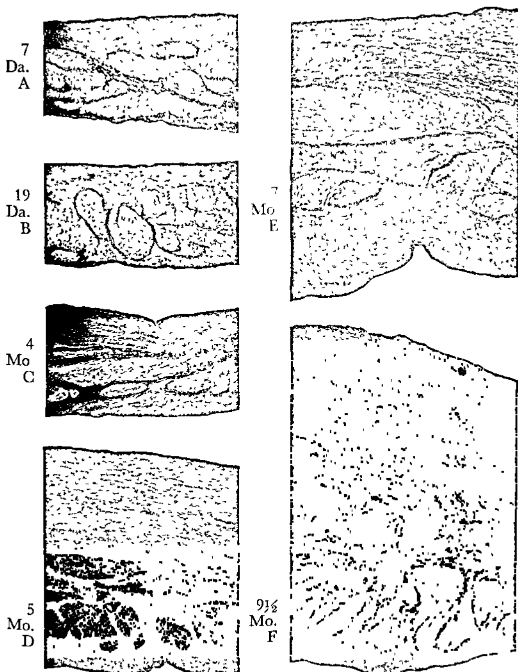


Figure II-42 Histologic changes in valvula foraminis ovalis following birth. (Photomicrographs, X 80) For comparable area, at birth, to same, see Figure II-41 (From Patten, *Am J. Anat*, Vol 48, 1931.)

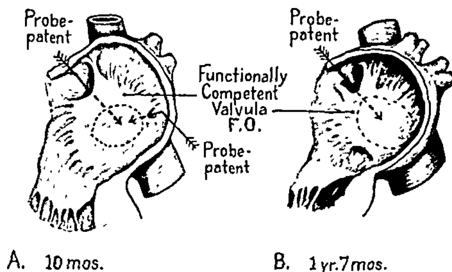


Figure II-43 Examples of hearts showing the foramen ovale guarded by a valvula ample in its overlap, but incompletely fused to the septum Such hearts show what may be designated as adequate functional closure with a persistent probe-patency. Probe-patencies of this type are apparently no functional handicap to an otherwise normal person and persist in from 20 to 25 per cent of all adults. (From Patten, *Am J Anat*, Vol 48, 1931)

secundum (Figure III-8). The thin interatrial wall of the fossa itself is septum primum, closing the fetal opening When *one inserts a probe under the margin of* the fossa ovalis to see whether or not it can be pushed all the way into the left atrium, one is but prying at the seal placed on the foramen ovale following birth.

The foregoing discussion of the postnatal occurrences at the ductus arteriosus and at the foramen ovale was predicated on the normal development of the lungs and their vessels. If there is any failure in the pulmonary system, the story is different. A blood stream, like any other fluid current, is bound to seek the path of least resistance. Normally when respiration in the lungs commences, the peripheral resistance of the pulmonary circulation is sufficiently reduced so that the blood pumped over the pulmonary trunk all goes to the lungs rather than forcing its way over the ductus arteriosus against the now higher pressure of the aortic stream If, through any deficiency in the development of the lungs themselves, or of their vessels, undue resistance to the free passage of blood exists, the pulmonary artery will continue to shunt a portion of its blood stream over the ductus arteriosus to the *aorta just as it did before birth. That this* happens but rarely is perhaps the most remarkable fact about the entire series of circulatory changes which take place at birth, for there is no way this peripheral part of the pulmonary circulation can be tested under functional conditions while the fetus remains *in utero.* Yet, the instances in which it fails the test of immediate functional adequacy at the time of birth are exceedingly few.

In the exceptional cases in which the pulmonary circulation does not at once begin to function properly, the entire balance within the heart is upset. The blood which fails to enter the lungs goes through the ductus arteriosus into the aorta and is returned by the systemic veins to the right atrium. The same process reduces the amount of blood which reaches the left atrium by way of the pulmonary veins. This causes a marked inequality in the volume of blood entering the two atria and a resultant inequality of the blood

pressure on opposite sides of the interatrial septum. Consequently, unoxygenated blood passes through the foramen ovale from right to left and the infant is *cyanotic. The primary cause of the difficulty is not,* as is so often misstated, the "failure of the foramen ovale to close at birth." Its structural closure is always a gradual process. It is open throughout fetal life or the embryo would not have sufficient left ventricular development to carry the systemic circulation, and it normally remains structurally unclosed for most of the first postnatal year. What does *occur in these cases is failure to establish* balanced pressure conditions which effect prompt functional closure, and at the same time facilitate the gradual structural closure of the foramen ovale.

With birth and the interruption of the *placental circuit there follows the gradual* fibrous involution of the umbilical vein and the umbilical arteries The flow of blood in these vessels, of course, ceases immediately with the ligation of the umbilical cord, but obliteration of the lumen is likely to take from three to five weeks, and isolated portions of these vessels may retain a vestigial lumen for much longer. Ultimately these vessels are reduced to *fibrous cords The old course of the um*bilical vein is represented in the adult by

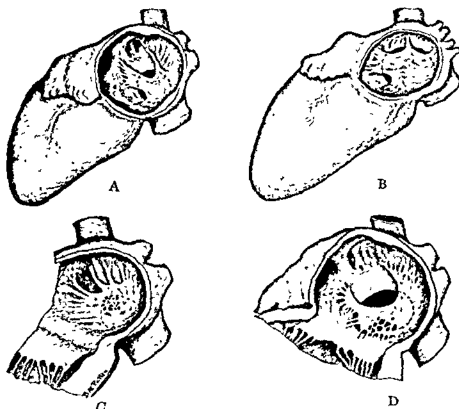


Figure 11 ... mechanism of foramen ovale which prevent effe... sorption of septum primum. (Stillborn, autopsy ... ct due to underdevelopment of septum secundum leaving an abnormally large foramen ovale (Female, lived 16 hours, autopsy 176,346, *Path Inst, Vienna*) C. Perforated valvula, resorption in abnormal locations. (Male, age three months, autopsy 176,312, *Path Inst, Vienna*) D Extensive valvular defect involving a combination of all three of the above factors (Specimen 4093, Rokitansky Museum, Vienna; from forensic autopsy of child aged about five months.) (From Patten, *Am J Path*, Vol 14. 1938)

the ligamentum teres from the umbilicus to the liver, and within the substance of the liver by the ligamentum venosus. The proximal portions of the umbilical arteries are retained in reduced relative size as the hypogastrics. The fibrous cords extending from these arteries on either side of the urachus toward the umbilicus are the remains of the more distal portions of the old umbilical arteries, known in the adult as the "obliterated branches" of the hypogastric arteries.

Much yet remains to be learned as to the more precise physiology of the fetal circulation and as to the interaction of various factors during the transition from intra-uterine to postnatal conditions Nevertheless, with our present knowledge it is quite apparent that the changes in the circulation which occur following birth involve no revolutionary disturbances of the load carried by different parts of the heart The fact that the pulmonary circulation is already so well developed before birth means that the changes which must occur following birth are far less profound than was formerly believed; and the compensatory mechanisms at the foramen ovale and the ductus arteriosus which have been functioning all during fetal life are entirely competent to effect the final postnatal rebalancing of the circulation with a minimum of functional disturbance. It is still true that as individuals we crowd into a few crucial moments the change from water-living to air-living that in phylogeny must have been spread over eons of transitional amphibious existence. But as we learn more about this change in manner of living, it becomes apparent that we should marvel more at the completeness and the perfection of the preparations for its smooth accomplishment, and dwell less on the old theme of the revolutionary character of the changes involved.

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CHAPTER III

The Structure of the Adult Heart

ALEXANDER BARRY AND BRADLEY M. PATTEN

THE HEART AS A WHOLE

Shape and Relations. The adult heart is a roughly conical, hollow, muscular organ with walls consisting of three layers: endocardium, myocardium, and epicardium (visceral pericardium). The epicardium is a serous membrane, continuous with the parietal pericardium which lines the pericardial cavity. The base of the heart is poorly circumscribed but corresponds in a general way with the area occupied by the great vessels entering and leaving the heart, together with that portion of the heart wall which lies between them. The heart is held in position within the pericardial cavity by these great vessels and the visceral pericardium (epicardium), which is reflected at their roots to become continuous with the parietal pericardium. Thus, the heart is not rigidly fixed within the pericardial cavity; during its contraction both its base and its apex undergo changes in position, and the heart as a whole is freely movable within the pericardial cavity.

The Chambers of the Heart. The heart is divided into four chambers: two thin-walled atria which serve as the intake chambers, and two heavy-walled ventricles the contractions of which carry out the effective pumping action of the heart. The interior of the heart is divided into right and left sides by a partition passing from base to apex. The cavity of each atrium opens into the cavity of its corresponding ventricle by way of an atrioventricular ostium. The right atrium receives blood from the superior and inferior venae cavae and the coronary sinus, and passes it on to the right ventricle, which pumps it into the pulmonary trunk. The left atrium

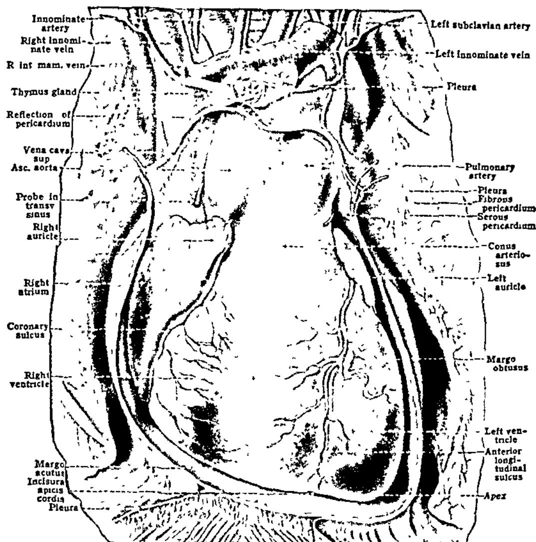


Figure III-1 Ventral view of heart *in situ* with the pericardial sac opened (After a dissection by R F Blount, drawn by Jean Hirsch, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia)

ceives blood from the four pulmonary veins, and passes it on to the left ventricle, which pumps it into the ascending aorta.

Terminology. In descriptions of the *anatomy of the heart confusion often arises* because of the terminology used in describing relationships Such terms as "in front of," "behind," "above," "below" are not sufficiently unequivocal for anatomic description. The terms "anterior" and "posterior" may be interpreted differently by different readers. In the following account the major axes will be described as *cephalic* and *caudal, dorsal* and *ventral,* and *right* and *left.* Although these terms lead to phrases that at times seem awkward, nevertheless they avoid ambiguity, and will be employed except where their use does violence to such venerable and *deeply rooted terms as "anterior* papillary muscle," or "anterior and posterior semilunar valves." In such instances consistency may well be sacrificed to tradition.

Orientation. Although the heart is commonly described as consisting of right and left halves, its longitudinal axis does not lie in the sagittal plane of the body. The apex of the heart points ventrally, to the left, and caudally. Its longitudinal axis forms an angle of approximately 40° with



Figure III-2 Teleroentgenogram of a cadaver, showing the relations of the heart, diaphragm, great vessels and ventral thoracic cage (After LeWald, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia) The atrioventricular, aortic and pulmonary ostia have been fitted with wire rings to show their respective positions In such embalmed preparations, these positions are about half an interspace higher than they are in the living erect subject

the horizontal, and is inclined to the right to form about the same angle with the sagittal plane. Therefore, the right and left atria do not lie cephalic to the corresponding ventricles but rather dorsal to, and to the right of them.

Size and Weight. In the average adult the heart measures about 12 5 cm (5 in) from base to apex, and 8 7 cm (3½ in) in its broadest dimension. In a man its weight is about 312 grams (11 ounces), and in a woman, about 225 grams (9 ounces) The weight of the heart makes up about 0.4 to 0 5 per cent of the total body weight of the average adult At birth it averages about 0 7 per cent of the total body weight In emaciated persons the heart weighs relatively more, and in the obese, relatively less The volume of the heart may be estimated in a living person by means of its x-ray silhouette *

EXTERNAL ASPECT OF THE HEART

Ventricular Portion. The apex of the heart is formed by the left ventricle The average position of the apex border in the erect individual is at the level of the sixth rib. This position in a series of 192 young adult men has been found to vary between the fifth rib and the sixth interspace (Woodburne and Whitaker, 1943) In the supine position, and in measurements in cadavers this location, like other similar relationships with skeletal landmarks, will

* If the area of this silhouette be determined in square centimeters, and appropriate correction be ...

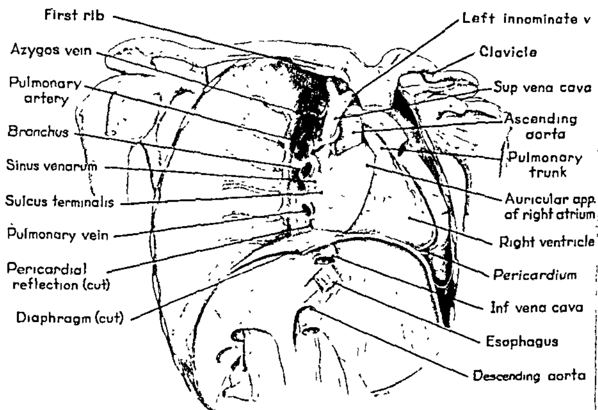


Figure III-3 Right anterior oblique view of the heart *in situ* The adjacent viscera have been removed, and the pericardial sac has been opened.

tend to be half an interspace higher. In hearts that have been hardened by fixation within the pericardial cavity, the conical regularity of the ventricular portion is disturbed by a well-marked triangular facet caused by contact with the diaphragm This area of contact, the so-called diaphragmatic surface, of necessity has a contour conforming to that of the upper surface of the diaphragm, and so faces caudally and slightly dorsally Its ventral margin is marked by an abruptly curved edge running from the apex to the right, as far as the right atrium. This margin is called the *margo acutus* (Figure III-1), and marks the transition between the diaphragmatic surface of the heart and its *sternocostal* surface, which faces the sternum and costal cartilages The dorsal edge of the diaphragmatic surface is more rounded than the *margo acutus*, and sweeps cephalically to form the dorsal side of the heart. The left surface of the ventricular portion of the heart is called the *margo obtusus*. It forms the rounded left side of the left ventricle, and extends from the ventricular apex to the root of the pulmonary trunk. The margo obtusus passes gradually over into the sternocostal surface of the heart.

The *interventricular sulcus* is a shallow groove which indicates, on the surface of the heart, the location of the internal partition separating the two ventricles. In it lie coronary blood vessels, nerves, and a variable amount of fat The part of this sulcus seen on the sternocostal surface is the *anterior longitudinal sulcus* (Figure III-1) which originates at the left of the root of the pulmonary trunk, runs obliquely over the upper part of the margo obtusus, and courses nearly vertically down over



Figure III-4 Right anterior oblique roentgenogram of the thoracic region of the adult, taken from essentially the same angle as the drawing in Figure III-3 (Courtesy of the Department of Roentgenology, University of Michigan)

the sternocostal surface As it crosses the margo acutus it forms a slight notch, the *incisura apicis cordis,* and is continued as the posterior longitudinal sulcus on the diaphragmatic surface.

The diaphragmatic surface is constituted about equally by the right and left ventricles, whereas the sternocostal surface is formed mainly by the right. The external line of demarcation between the atria and the ventricles is the *coronary sulcus* On the diaphragmatic surface of the heart, this groove is occupied by the *coronary sinus* It is well marked along the lateral and ventral aspects of the heart where it contains coronary arteries and veins, embedded in a considerable amount of fat.

Atrial Portion. The atrial portion of the heart lies to the right of, dorsal, and slightly cephalic to the ventricular portion. On the dorsal surface of the heart the division into right and left atria is not clearly indicated except in distended hearts, in which it is marked by a groove connecting the left sides of the superior and inferior venae cavae Ventrally the right and left auricular appendages of the atria protrude to bound a deep notch in which lie the ascending aorta and the pulmonary trunk. On the dorsal aspect of the right atrium a slight groove is seen connecting the right sides of the superior and inferior venae cavae This is called the *sulcus terminalis* (Figures III-3 and III-16) and represents the lateral boundary of what was the right horn of the embryonic sinus venosus which has been partially incorporated into the dorsal wall of the right atrium of the adult heart, forming the so-called *sinus venarum* (Figures III-3 and III-5).

The *superior vena cava* enters the right atrium cephalically while the *inferior vena cava* enters it from its caudal aspect The axes of these two great veins are nearly in line with each other and with the vertical axis of the body. The coronary sinus originates by confluence of venous tributaries below the left caudal pulmonary vein, and courses in the coronary sulcus caudally, dorsally, and to the right, to enter the right atrium slightly nearer the right atrioventricular ostium than the entrance of the inferior vena cava. The pulmonary veins course transversely and somewhat cephalically to enter the right and left sides of the left atrium (Figures III-5 and III-6).

Arterial Outlets of the Heart. Viewed in ventral aspect, the right ventricle can be seen to extend cephalically and slightly to the left, bounded by the anterior longitudinal sulcus and the coronary sulcus At the level between the second and third costal cartilages on the left, the pulmonary cone of the right ventricle gives rise to the *pulmonary trunk* (Figure III-1). This vessel curves abruptly dorsally, and after a distance of about one and one-half inches (4 3 cm) bifurcates into right and left pulmonary arteries. The pulmonary tr

is commonly referred to in clinical literature as the "undivided portion of the pulmonary artery," a prolixity that has little to recommend it.

The left ventricle discharges into the ascending aorta slightly to the left of the midline, at about the level of the attachment of the third costal cartilage. The orifice of the aorta lies dorsal, caudal, and slightly to the right of the pulmonary trunk (Figure III-19). The aorta may be divided into three portions for descriptive purposes: (1) the ascending aorta, running cephalically and very slightly to the right, (2) the aortic arch, which swings dorsally and to the left, arching over the right pulmonary artery and the bifurcation of the pulmonary trunk; and (3) the descending aorta, which passes caudally and, in its thoracic extent, lies to the left of the midline From the aortic arch arise the large arteries that supply blood to the upper part of the body: the innominate, the left common carotid and the left subclavian A ligament, about 3 to 5 mm. in diameter and from 8 to 15 mm. in length, connects the left pulmonary artery to the aortic arch. This is called the *ligamentum arteriosum* (Figure III-28). It is of importance as a landmark since it represents the fibrous remains of the ductus arteriosus of the fetus (Figures II-34 and II-39). It is attached to the cephalic aspect of the left pulmonary artery close to the bifurcation of the pulmonary trunk. It passes dorsally, slightly cephalically and to the left, to attach to the aortic arch on its caudal side slightly caudal to the origin of the left subclavian artery. One of the less uncommon anomalies of cardiac development is persistence of a patent ductus arteriosus. Such a retained fetal channel will have essentially the same relations as the ligamentum arteriosum of the normal adult, although there is a tendency for a patent ductus arteriosus to become shortened, a point of some surgical significance.

THE PERICARDIAL CAVITY

The heart, except for attachments at its venous and arterial ends, lies free within the pericardial cavity. This cavity is lined by a serous membrane, the pericardium, consisting of a mesothelial layer and an underlying fibrous lamina. At the regions where the heart is attached to the dorsal thoracic wall, the pericardium lining the wall of the pericardial cavity is reflected over the heart. In this position it is called the visceral pericardium or more commonly, by histologists, the epicardium. The positions of these lines of reflection are shown in Figures III-3, III-5 and III-6. Their embryologic derivation is indicated in Figures II-29 and II-33 There are essentially two regions of reflection, one surrounding the ascending aorta and the pulmonary trunk, and the other surrounding the great veins entering the atria. The pericardial reflection surrounding the venous inlets forms a mesentery-like membrane (mesocardium), which passes between the dorsal wall of the pericardial cavity and the heart, and encloses the several inlets in a common investment It has a cephalocaudal portion which extends between the caval inlets and includes the roots of the right pulmonary veins It sweeps transversely from the right to the left superior pulmonary vein, and turns caudally to envelop the root of the left inferior pulmonary vein. This horseshoe-shaped line of reflection partially isolates a portion of the pericardial cavity which is called the *oblique sinus* (Figures II-33E and III-6). The ring of pericardial reflection surrounding the ascending aorta and

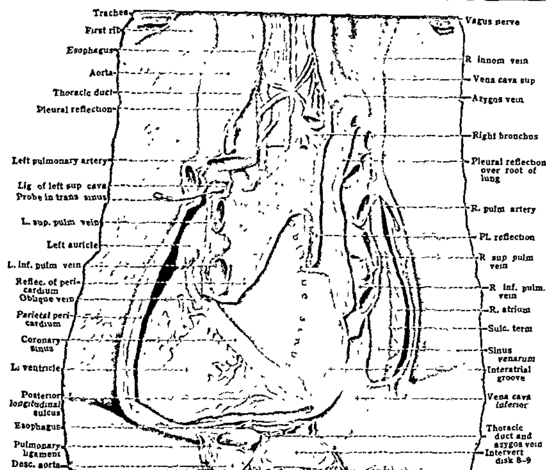


Figure III-5 Dorsal view of the heart *in situ* The pericardial sac has been opened in such a manner that its reflections around the roots of the great vessels are emphasized (After a dissection by R F Blount, drawn by Jean Hirsch, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia)

the pulmonary trunk is independent of the mesocardial complex surrounding the venous inlets There is, therefore, a portion of the pericardial cavity running transversely across the midline immediately cephalic to the superior pulmonary veins and the superior vena cava. This is called the *transverse sinus* of the pericardial cavity It represents in the adult the place where the embryonic dorsal mesocardium first broke through to make the right and left coelomic cavities confluent across the midline

In some persons the left common cardinal vein (duct of Cuvier) may persist in the adult This condition is usually spoken of as a double superior vena cava. Ordinarily in such cases there is present a left innominate vein of reduced size, and the left superior cava which enters by way of the coronary sinus is smaller than the right. Occasionally, by reason of a complete failure of the innominate to develop as a shunt from the left to the right anterior cardinal vein (Figure II-12), the two superior cavae may be of equal size, thus retaining the primary bilateral symmetry of the embryonic venous system (Prows, 1943) More commonly the left common cardinal vein is reduced in size, and persists in the adult as a small vein coursing obliquely across the dorsal aspect of the left atrium, to the left of th pulmonary veins (Marshall, 18

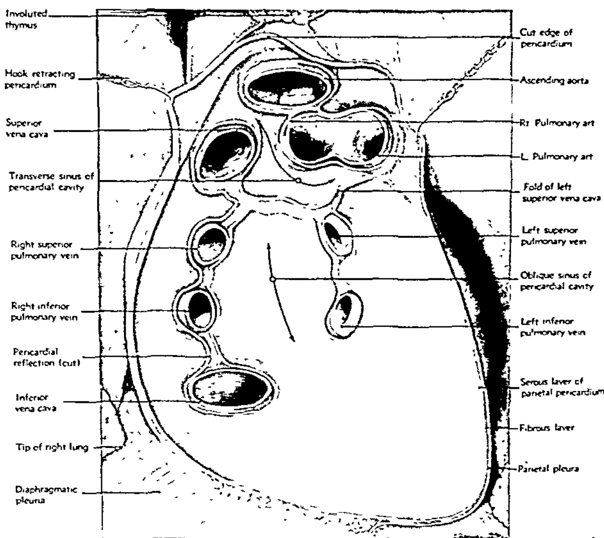


Figure III-6 Dorsal wall of the pericardial cavity. The heart has been removed in such a manner as to show the reflections of the pericardium around the roots of the great vessels (See Figure II-33)

is called the *oblique vein of the left atrium* or oblique vein of Marshall (Figures II-29 and III-16). This vein may be continued cephalically as a small vein, or more commonly as a fibrous cord, to attach to the left highest intercostal vein. The parietal pericardium is usually pulled up into a fold by this vein or ligament to form the vestigial fold of the left superior vena cava (vestigial fold of Marshall). The vestigial fold of Marshall originates near the left entrance *into the transverse sinus of* the pericardial cavity, and can be traced cephalically and to the left (Figure III-6). The attachment of this mesocardial fold to the dorsal wall of the pericardial cavity is not always found to the left of the left superior pulmonary vein as might be expected from the course of the oblique vein of Marshall, but may be secondarily displaced to the right so that it is situated within the transverse sinus itself.

The pericardial cavity of the normal adult contains about 25 or 30 cc. of pericardial fluid. This is a straw-colored serous fluid with essentially the composition of lymph. *It serves to minimize* friction between the visceral and parietal layers of the pericardium.

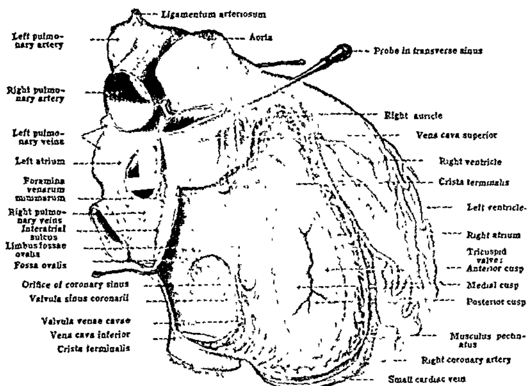


Figure III-7 . . . versed heart, with the right atrium opened to show its internal . . . re with Figure III-3 (After a dissection by R F Blount The . . . been slightly modified, from Morris' *Human Anatomy*, courtesy of the Blakiston Company)

THE INTERIOR OF THE HEART

The Interatrial Septum. The interior of the atrial portion of the heart is divided by the interatrial septum into right and left chambers This septum is a composite structure, being derived from two independent septa of the embryonic atrium, neither one of which was formed as a complete partition in itself (Figures II-16, II-18 and II-19). The openings in the two embryonic septa do not normally coincide in position, so that when fusion of the septa is completed, usually during the first year of postnatal life, the impervious partition characteristic of the adult heart is formed Traces of the two originally independent parts of the interatrial septum are, however, clearly recognizable in the adult. The crescentic margin of the old *valvula foraminis ovalis*, can be seen more or less firmly adherent to the left side of the septum (Figure III-10). The area cephalic to this margin represents the location of ostium II of interatrial septum primum of embryologic descriptions (Figure II-28). The main muscular part of the interatrial septum is derived from a septum (interatrial septum secundum) that forms somewhat later, immediately to the right of the septum primum Septum secundum retains throughout fetal life an oval opening called the foramen ovale, the margin of which is seen on the right side of the adult interatrial septum as the *limbus fossae ovalis*. After the valve of the foramen ovale (septum primum) has fused to the lef atrial side of the septum secundum, t

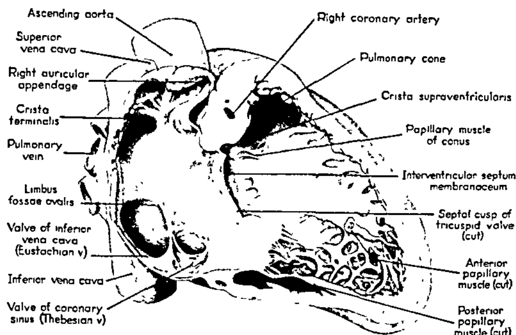


Figure III-8 Right side of the heart opened in a plane approximately parallel to the septa, to show the interior of the right atrium and the right ventricle A segment of the septal leaflet of the tricuspid valve has been cut away to expose more fully the region of the membranous portion of the interventricular septum

foramen ovale becomes a more or less oval depression on the right side of the interatrial septum, called the *fossa ovalis* (Figure III-8). In some 20 to 25 per cent of adult hearts the fusion of the valve of the foramen ovale with the septum secundum is not complete By following the direction of the inferior vena cava, a slender probe may be slipped under the limbus fossae ovalis, between the valve of the foramen ovale and the muscular portion of the septum, into the left atrium. This condition, characterized as "probe-patency" (Figure II-43), is discussed in Chapter II Such openings are vestiges of an important fetal blood route which is abandoned postnatally, after the lungs have become completely functional Failure of complete fusion between the two parts of the embryonic interatrial septum with resulting probe-patency does not appear to be a handicap to an otherwise normal heart, and is of sufficient frequency to be regarded as a variant of the normal Probe-patency should be sharply distinguished from a true valvular defect such as exists when the valve of the foramen ovale is incompetent to guard the foramen ovale.

The Right Atrium. The inferior vena cava passes through the diaphragm and enters the caudal side of the right atrium (Figures III-3 and III-8). The inferior caval orifice is partially guarded along its ventral aspect by an incompetent valve flap of variable fullness, the *valve of the inferior vena cava* (eustachian valve). Dorso-caudally on the wall of the right atrium, between the atrioventricular orifice and the fossa ovalis, is located the opening of the coronary sinus, guarded by the *valve of the coronary sinus* (thebesian valve). Leading from the right atrium ventrally, slightly caudally, and to the left is the right atrioventricular orifice which is guarded by the tricuspid valve. Extending between the right sides of the superior and inferior caval orifices there is a prominent muscular ridge, the *crista terminalis* (Figure III-8), which underlies the sulcus terminalis As the crista terminalis

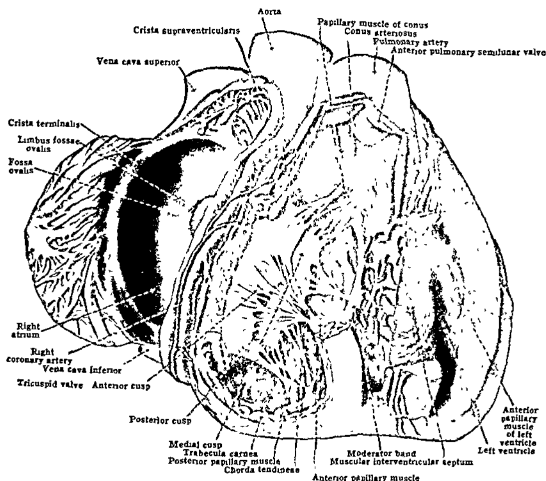


Figure III-9 Ventral view of the heart with the walls of the right atrium and ventricle opened to show their internal configuration The dissection was planned to show the relations of an unusually well developed moderator band In this heart the position of the foramen ovale is somewhat more cephalic than usual (After a dissection by R F Blount, drawn by Jean Hirsch, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia)

extends caudally it becomes less distinct. Its general course is continued by the valve of the inferior vena cava. Cephalically the crista terminalis passes to the right of the orifice of the superior vena cava, and continues as a muscular ridge which forms the sinistral margin of the opening into the *right auricular appendage* (Figure III-9) This appendage projects cephalically from the right atrium (Figure III-8) and lies in contact externally with the ascending aorta (Figure III-1). The interior of the right auricular appendage is trabeculated by muscular bands, the pectinate muscles. These appear to arise from the most cephalic part of the crista terminalis, and radiate out over the inner surface of the auricular appendage, forming the shell-like pattern which has given them their name.

The portion of the right atrium bounded laterally by the crista terminalis, and medially by the interatrial septum is smooth-walled, and is called the *sinus venarum.* It is the adult derivative of the enlarged right horn of the sinus venosus of the embryo (Figure II-29). The lower part of the crista terminalis marks the original line of attachment of the upper part of the right sinus valve; the part of the crista lying cephalic to the superior vena cava, on the cephalic wall of the atrium, is derived from the ex-

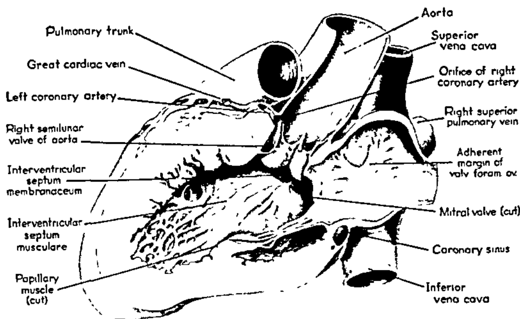


Figure III-10 Left side of the heart opened in a plane approximately parallel to the septa, to show the interior of the left atrium and left ventricle A segment of the anterior leaflet of the mitral valve has been cut away to expose more fully the region of the membranous portion of the interventricular septum and the aortic orifice

tension of the venous valves, especially the right one, which was known in the embryo as the septum spurium (Figure II-16B). The caudal portion of the right venous valve persists in reduced form as the (eustachian) valve of the inferior vena cava, and the (thebesian) valve of the coronary sinus. These valves vary considerably in size in different individuals and frequently show multiple small perforations. Occasionally lace-like strands from the margins of these valves may project far into the atrial lumen Usually they are continuous with similar strands inserting into the atrial wall along the line of the crista terminalis. Such a fibrous meshwork represents an incomplete resorption of septum spurium and the right venous valve When extensive, it presents a highly characteristic appearance and is known as Chiari's net Figure V-10A, B, page 283). The left valve of the sinus venosus usually disappears by blending with the interatrial septum In rare instances remnants of its upper portion may be found closely adherent to septum secundum, or even extending across the limbus fossae ovalis to lie against the valvula foraminis ovalis (Figure V-10C, page 284). Exceedingly rarely there may be lace-like remains of the extreme lower *portion of the left valve which may show* some continuity with remnants of the right valve around the coronary sinus.

The orifice of the superior vena cava is directed caudally and is unguarded by any valve. Across the inner face of the dorsal wall of the sinus venarum there is a transverse muscular ridge of variable prominence – the torus intervenosum (of Lower). Opening into the right atrium, particularly upon its septal and lateral walls, are numerous small openings, the foraminae venarum minimarum (thebesii).

Left Atrium. The left atrium is situated to the left of, and somewhat dorsal to, the right atrium. It lies dorsal to the root of the aorta, and its auricular appendage protrudes to the left of the pulmonary trunk. Opening into the dorsal wall of the left atrium are the right and left superior and inferior pulmonary veins. The orifices of these four veins are not guarded by valves

The left atrioventricular ostium, guarded by the mitral valve, lies on the ventral side of the atrium, facing slightly caudally and to the left. The inner face of the left atrium is relatively smooth, but the inner surface of the left auricular appendage is distinguished by well-marked pectinate muscles

Left Ventricle. In the adult the left ventricle has the form of a narrow cone, tapering to form the apex of the heart. The left ventricle forms the gently curved left cephalic border of the heart (margo obtusus), about half of the diaphragmatic surface, and a small part of the sternocostal surface.

The greater part of the inner surface of its wall is thrown into myocardial ridges of variable size. These ridges (trabeculae carneae) may either stand out in relief, or be undercut so that they form muscular bands completely covered by endocardium In general the myocardium of the left ventricle consists of an outer zone of relatively solid muscle that makes up about two-thirds of its thickness, while its inner third is trabeculated.

In the heart of the fetus and the newborn infant the left ventricular wall is no thicker than the right, and the interventricular septum forms a nearly straight partition between the two ventricular cavities However, after birth, with the complete separation of the pulmonary and the systemic vascular circuits, the left ventricular myocardium begins to assume its characteristic preponderance. By the fourth year the adult proportions are attained, and the left ventricular wall has approximately twice the thickness and three times the mass of the right (Muller, 1883).

Right Ventricle. In contrast with the wall of the left ventricle, the trabeculated part of the right ventricular wall makes up approximately two-thirds of its thickness and only its outer third is solid. The cephalic part of the right ventricle leading into the pulmonary trunk is called the *pulmonary cone* (Figure III-8), and is delimited from the rest of the right ventricular cavity by a muscular ridge, the supraventricular crest (crista supraventricularis) The main portion of the right ventricular chamber is crescentic in cross section, since the interventricular septum is concave on its left side and convex on its right (Figure III-12).

Interventricular Septum. The interventricular septum (ventricular septum) is thick and muscular except for a small area of connective tissue (pars membranacea), near the root of the aorta (Figures III-10, III-20 and III-22). From the left, this membranous portion can be seen to lie in the angle between the attachments of the right and the noncoronary cusps of the aortic semilunar valve. On the right side, the pars membranacea is partly concealed by the septal cusp of the tricuspid valve, the attachment of which courses across it near its atrial margin (Figures III-8 and III-25). The part of the septum membranaceum above the attachment of the septal leaflet of the tricuspid valve is, therefore, atrioventricular, since it lies between the right atrium and the left ventricle (Figure III-11). The membranous portion is the last part of the ventricular septum to be formed embryologically, and is of especial interest clinically since it is the most common site of interventricular defects It is often referred to by British authors as the "undefended space"

On the left ventricular face of the septum one can occasionally make out the course of the fibers of the *left branch of the atrioventricular bundle* (of His), as they fan out immediately beneath the endocardium. These bundles of fibers can be seen to emerge at the apical margin of the septum membranaceum (Figure III-26). It is known from microscopic study that these fibers of the left branch of the bundle of His spread out in flattened fascicles over the interventricular septum mu-

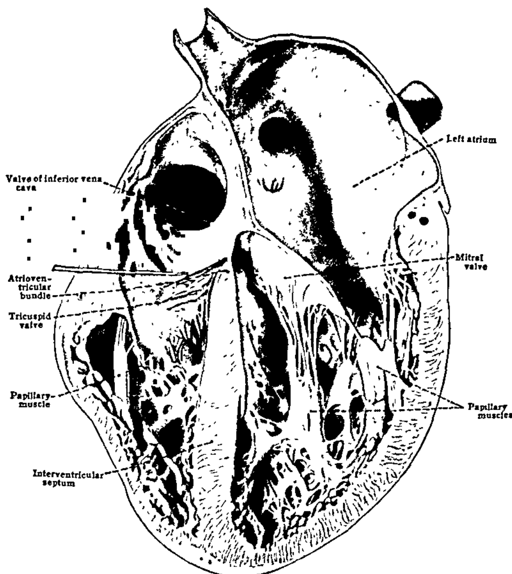


Figure III-11 Frontal section through a heart fixed in diastole, showing a ventral view of the dorsal portion The plane of section passes through the septum membranaceum and both atrioventricular ostia. (After Tandler, from Morris' *Human Anatomy*, courtesy of Julius Springer and The Blakiston Company)

lare. However, their extent and precise course cannot be determined with certainty by gross inspection, since these specialized fibers are macroscopically indistinguishable from bundles of typical cardiac muscle of the interventricular septum.

A large muscular trabecula is sometimes found to extend from the septal wall of the right ventricle to the base of the anterior papillary muscle. This is called the *moderator band* (Figure III-9). When this band is present it regularly contains a part of the right branch of the atrioventricular bundle. The moderator band is clearly distinguishable in the hearts of some persons, while in others it appears as a prominent ridge (crista septo-marginalis), and in still others is not differentiated at all.

Papillary Muscles. Two papillary muscles of the right ventricle are relatively constant in position, a large anterior papillary muscle, and a smaller papillary muscle of the conus (of Luschka) (Figure III-8). The *anterior papillary muscle* is situated

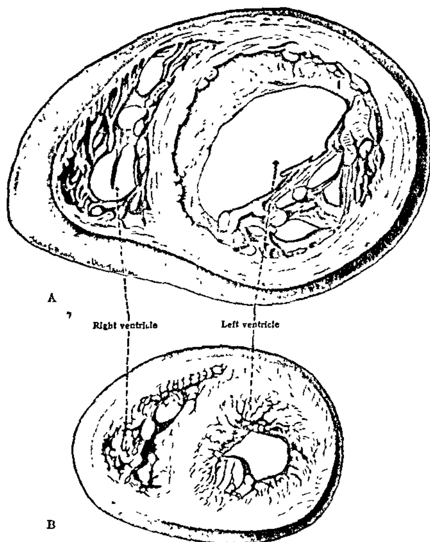


Figure III-12 Sections of the heart cut through the ventricles to show their change in configuration during contraction (After Tandler, from Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia)

on the ventral wall of the right ventricle near its junction with the septal wall The *papillary muscle of the conus* lies just below the septal end of the crista supraventricularis (Figure III-8). A group of *posterior papillary muscles* which are inconstant in number and position arise from the diaphragmatic wall of the ventricle. Some chordae tendineae stretch directly from the septal wall, with or without papillary elevations at their base, to the septal leaflet of the tricuspid valve. The chordae tendineae from the anterior papillary muscle run to the ventral and dorsal leaflets, those from the papillary muscle of the conus run to the septal and ventral, and those from the posterior papillary muscles run to the septal and dorsal leaflets of the tricuspid valve. In the left ventricle there are two large papillary muscles of relatively constant position – the anterior and posterior. Both of these send chordae tendineae to each of the leaflets of the mitral valve.

Atrioventricular Valves. The atrioventricular valves are attached around the orifices leading from the atria into the ventricles and their leaflets extend into the

cavities of the ventricles. Each valve has a continuous line of attachment, but its free edge is notched, partially subdividing it into leaflets (Figure III-19) The right atrioventricular valve is usually divided into three leaflets and is, therefore, called the tricuspid valve. The left atrioventricular valve is similarly divided, but into two leaflets and is called the bicuspid or, from its fancied resemblance to a bishop's miter, the mitral valve. The depth of the notches in both of these valves is extremely variable, and there may be an increase or, more rarely, a decrease in the number of leaflets. Each valve leaflet is attached to the ventricular papillary muscles or directly to the ventricular wall by fibrous cords, the chordae tendineae, which are generally branched and of varying thickness. The thinnest cords are attached to the free edge of the leaflet, those of intermediate thickness to its ventricular surface a few millimeters from its free margin, and the thickest are attached to the ventricular surface near the attached border of the leaflet. The valves are smooth and glistening on their atrial aspect but, because of the attachment of the chordae tendineae, are irregular and fasciculated on their ventricular surface (Figures III-21 and III-22). The leaflets of the mitral valve are called ventral (anterior) and dorsal (posterior). Those of the tricuspid are called anterior, posterior, and medial (ventral, dorsal, and septal) (Figure III-19). Each leaflet receives chordae tendineae from more than one papillary muscle, and each papillary muscle sends chordae tendineae to more than one valve leaflet. The chordae tendineae of the mitral valve are heavier than those of the tricuspid The chordae tendineae and papillary muscles combine to prevent the leaflets of the atrioventricular valves from being forced back into the atria by the pressure built up in the ventricles during systole. Contraction of the papillary muscles, along with the rest of the ventricular musculature, prevents a slackening of tension on the chordae tendineae which would otherwise occur when the ventricular cavity becomes smaller during ventricular systole.

Semilunar Valves. The outlet of each ventricle is guarded by three semilunar valve cusps, each of which is a pocketlike flap of connective tissue, covered by endothelium and attached to the annulus fibrosus of the aorta or the pulmonary trunk. The free edges of these cusps are directed away from the ventricle, and in the center of each there is a small fibrocartilaginous *nodule*, the *corpus arantii*. Radiating from this nodule over the fundus of the cusp and extending to its attached margin are fibrous thickenings. On either side of the nodule the free edge of each cusp is thin, forming a pair of crescentic areas called the *lunulae* (Figures III-10 and III-22).

There are two widely employed systems of naming the cusps of the semilunar valves. If they are named according to their relative positions when the heart is *in situ* in the thorax, as is done in one system, the aortic valves are named *right posterior, left posterior,* and *anterior;* while those of the pulmonary trunk are named *right anterior, left anterior,* and *posterior* (Figure III-13B) However, if the heart is removed from the body and held so that the ventricular septum forms its median plane, the pulmonary trunk lies almost directly ventral to the aorta, and the valves of the pulmonary trunk are named *right posterior, left posterior,* and *anterior;* while those of the aorta are named *right anterior, left anterior, and posterior* or *noncoronary* (Figure III-13A). This latter terminology, although not consistent with the axes used in naming some other regions of the heart, is convenient in that it corresponds to the naming of the right and left ventricles, and the right and left coronary arteries. It is also the more logical from a developmental point of view.

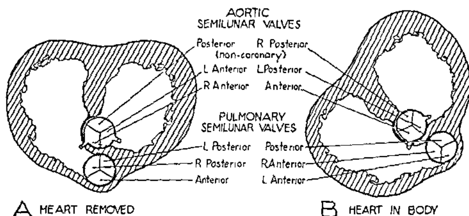


Figure III-13 Diagrams showing the bases for the two common systems of naming the semilunar valves A, based on a removed heart oriented with its ventricles to the right and left of the septum This is the B N A system B shows the names of the cusps, based on their relative positions with the heart *in situ* in the adult thorax This is the I N A system

The aortic semilunar valves are stronger than those of the pulmonary trunk, as might be expected from the higher pressure in the aorta. Opposite these aortic semilunar valves, the aortic wall bulges out into three corresponding dilations, called the aortic sinuses or sinuses of Valsalva (Figure III-22). The right and left coronary arteries arise from the upper part of the right and left aortic sinuses, respectively (Figure III-19)

THE BLOOD VESSELS OF THE HEART

Coronary Arteries. The *left coronary artery* arises in the wall of the left sinus of Valsalva and runs laterally and ventrally between the root of the pulmonary trunk and the left atrium. After a short distance it branches into two vessels, the *anterior descending branch*, which courses caudally in the anterior longitudinal sulcus to reach the apex of the heart, and the *circumflex branch*, which swings around the base of the left atrium, in the coronary sulcus, to reach the diaphragmatic surface of the heart (Figure III-14). In its course the anterior descending branch sends perforating rami into the substance of the interventricular septum and into the adjacent ventricular myocardium. The circumflex branch gives off a ramus which runs down over the margo obtusus toward the apex of the heart, and also sends off many other smaller arteries to supply the root of the aorta, left atrium, and left ventricular wall To the left of the posterior longitudinal sulcus, adjacent to the coronary sinus, the circumflex branch anastomoses with small arteries from the right coronary artery (Figure III-16).

The *right coronary artery* arises from the right aortic sinus and passes laterally in the groove between the pulmonary cone and the right atrium (Figure III-15) It then sweeps, in the coronary sulcus, around the base of the right atrium to reach the posterior longitudinal sulcus At this point it divides, sending a large branch along the length of the posterior longitudinal sulcus which is known as the *posterior descending branch*, and a smaller branch to anastomose, adjacent to the coronary sinus, with the circumflex branch of the left coronary artery (Figure III-16). The first ventricular branch of the right coronary artery passes to the musculature of the pulmonary cone. This has been r

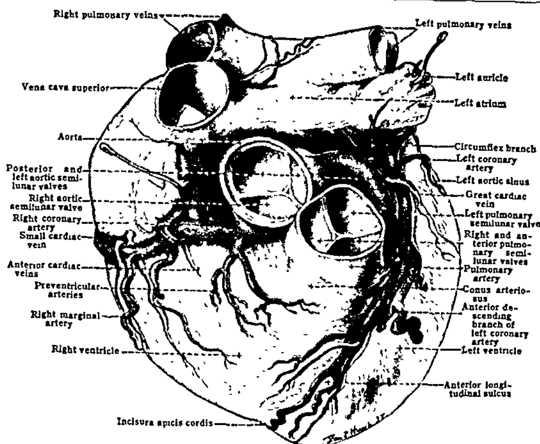


Figure III-14 Cephalic view of the heart with the epicardium removed to expose the injected coronary vessels (After a dissection by R F Blount The original drawing by Jean Hirsch has been slightly modified, from Morris' *Human Anatomy*, courtesy of The Blakiston Company)

ported to arise independently from the right sinus of Valsalva in one-half of a series of adult hearts (Schlesinger, Zoll and Wessler, 1949). In its course the right coronary artery gives off two sizable branches, one to run along the margo acutus, the *right marginal*, and another to pass over the ventral wall of the right ventricle, the *preventricular* (Figure III-14). It also gives off smaller branches to supply the roots of the aorta, the pulmonary trunk, and the right atrium. A small but constant branch passes between the right auricular appendage and the superior vena cava to course along the sulcus terminalis. This branch is of importance since it lies along the axis of the sinoatrial node. The posterior descending branch gives off perforating rami to supply the muscle of the interventricular septum and the adjacent ventricular walls.

The study of the terminal branches of the coronary arteries of the human heart by means of gross dissection, even of well-injected specimens, is laborious and necessarily incomplete. In recent years a method has been devised in which the coronary arteries are injected with a radio-opaque medium. Following this injection the heart is cut and "unrolled" or flattened out so that a roentgenogram may be made of the entire arterial pattern of the walls of both ventricles and part of the atria The interventricular septum may be cut free at its attached borders and photographed on the same x-ray film to give a complete picture of the arterial supply of the entire ventricular myocardium (Schlesinger, 1938; Salans and Tweed, 1947). Such studies show that adult human hearts vary considerably with respect to the relative distribution of the branches of the

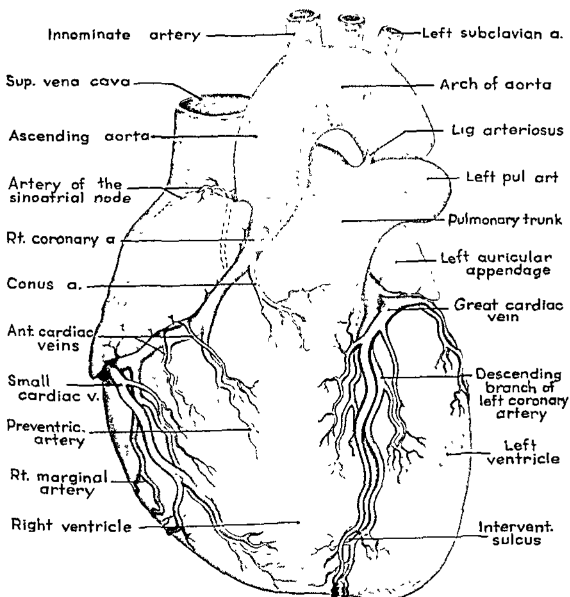


Figure III-15 Ventral view of the heart with the epicardium removed to expose the injected coronary vessels

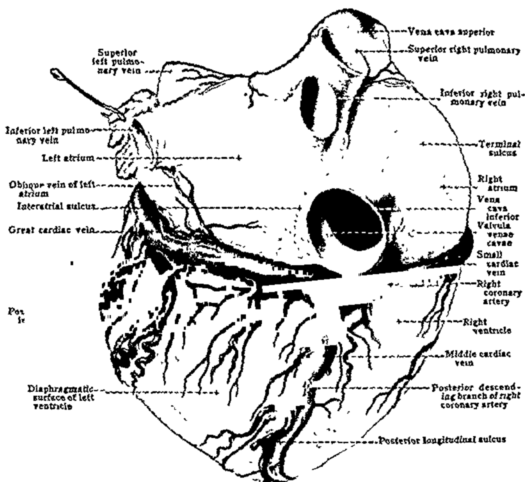


Figure III-16 Dorsocaudal view of the heart with the epicardium removed to expose the injected coronary vessels (After a dissection by B F. Blount The original drawing by Jean Hirsch has been slightly modified. From Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.)

right and left coronary arteries. Hearts may be classified into one of three groups, according to whether the right or left coronary arteries predominate. Group I consists of hearts in which the right coronary predominates; in Group II the right and left coronaries are balanced in distribution, and in Group III, the left coronary is dominant. In a study by Schlesinger (1940), Group I made up 48 per cent of a series of 225 adult hearts; Group II, with a balanced circulation, made up 34 per cent; and the remaining 18 per cent fell in Group III, with a predominant left coronary artery It is of interest that the dominant artery supplied nearly all of the musculature of the interventricular septum.

Coronary Veins. The coronary veins lie parallel to the branches of the coronary arteries, and return the blood to the right atrium by way of the coronary sinus. In general they lie in the fat-laden connective tissue of the epicardium, somewhat superficial to the arteries.

The *great cardiac vein* originates in the epicardium of the anterior longitudinal sulcus (Figure III-14). When it reaches the coronary sulcus it swings dorsally and, within it, courses around the base of the left atrium in company with the circumflex branch of the left coronary artery. It empties into the distal end of the coronary sinus beneath the left inferior pulmonary vein (Figure III-16). At this point there is usually a pair of valves. In its

course it receives from the walls of the left atrium and ventricle tributaries, most of which are guarded by valves at their points of confluence with it.

The *middle cardiac vein* runs in the posterior longitudinal sulcus in company with the posterior descending branch of the right coronary artery. It receives blood from the septum and the ventricular walls and empties into the coronary sinus near the opening of the coronary sinus into the right atrium. Its orifice is usually guarded by a single valve.

The *small cardiac vein* lies in the coronary sulcus at the base of the right atrium Through much of its course it parallels the right coronary artery. It receives tributaries from the walls of the right atrium and ventricle and empties into the coronary sinus near its entrance into the right atrium (Figure III-16).

The *posterior vein of the left ventricle* runs over the dorsal aspect of the ventricle to empty into the coronary sinus near its distal end. There are similar small unnamed veins draining the diaphragmatic surface of the left ventricle and discharging into the coronary sinus

The *anterior cardiac veins* lie on the ventral aspect of the right ventricle, and empty either into the small cardiac vein, or directly into the right atrium (Figure III-14).

There is a small vein that passes down over the dorsal wall of the left atrium, lateral to the left pulmonary veins, and empties into the distal end of the coronary sinus This is the oblique vein of the left atrium or vein of Marshall (Marshall, 1850). It is highly variable in size, and represents the left common cardinal vein of the embryo (Figure II-29). It is this vessel which is the terminal portion of a left superior vena cava, when such a vessel persists (see Chapter II, page 58).

The Intramural Circulation. The myocardium is richly supplied with small vascular channels There is an extensive web of capillaries which course among the cardiac muscle fibers, and lie in intimate contact with them These capillaries are fed by branches of the various coronary arteries, and are drained in part by the coronary veins whose epicardial pattern has been described above However, there is a peculiarity of the intramyocardial circulation which deserves particular attention. Careful injection studies show that there are anastomosing vessels which run between adjacent branches of the same coronary artery, between branches of the right and left coronary arteries, between the coronary arteries and the coronary veins, and between branches of the coronary veins (Figure III-17) (Schlesinger, 1938, Gross, 1921, Prinzmetal *et al*, 1947, 1948) It seems probable that in the normal heart of a young person these anastomoses are small, since it is well known that in case of sudden occlusion, branches of the coronary arteries behave as end arteries and their occlusion leads to infarction of the myocardium. Nevertheless, these anastomoses are capable of gradual enlargement, and in many hearts may be found to be functionally of significant caliber In addition, the intramyocardial vascular pattern exhibits another peculiarity There are channels which pass from the arterioles, from the capillary bed, and from the coronary veins directly into the lumen of the heart (Figure III-18). These venous connections with the cardiac lumen have been described for many years as the *thebesian veins* (Thebesius, 1716). The connections between the coronary arteries and the cardiac chambers, called *arterio-luminal vessels,* have been found more recently (Wearn, 1928a; Wearn *et al*, 1933). Since the walls of the ventricles are thrown into trabeculae, these arterio-luminal vessels may empty either at the surface of the trabeculae or, as is more usual, into the intertrabecular spaces.

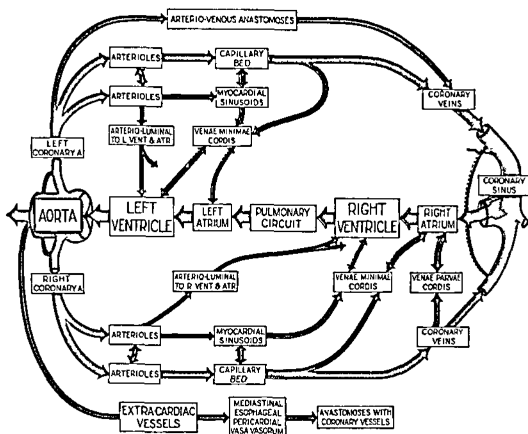


Figure III-17 Schematic plan indicating the interrelations of the various vascular channels supplying the walls of the heart. (Developed in collaboration with Richard Licata)

The arterio-luminal vessels have the histologic characteristics of venous channels when they pass through the endocardium At a variable depth within the myocardium they acquire the muscular coat typical of an artery. Accordingly these arterio-luminal vessels may reasonably be regarded as *venae minimae cordis* (thebesian veins) which are connected directly to the coronary arteries by means of arterio-venous anastomoses of arteriolar caliber.

Deep within the myocardial musculature there is, in addition to the capillary bed (Wearn, 1928b), a richly anastomosing network of thin-walled irregular channels which have been called *myocardial sinusoids*. These sinusoids receive vessels from the coronary arteries and the capillaries, and communicate with the coronary veins. From their developmental history, these *myocardial sinusoids may be regarded as* intertrabecular spaces of much reduced caliber. If they are so regarded, their interconnections with the coronary vessels and their continuity at the same time with the intertrabecular spaces of the lumen of the heart are reasonable and consistent. Figure *III-18 shows these interrelationships* in schematic form.

The Lymphatics. There are two networks of lymphatics in the heart, one in the endocardium and the other in the epicardium. The endocardial network drains through channels in the myocardium into the lymphatics of the epicardium. The epicardial meshwork of channels, containing many valves, drains toward the atrioventricular sulcus by means of several longitudinal channels which run for the most part parallel to the coronary veins in the anterior and posterior longitudinal

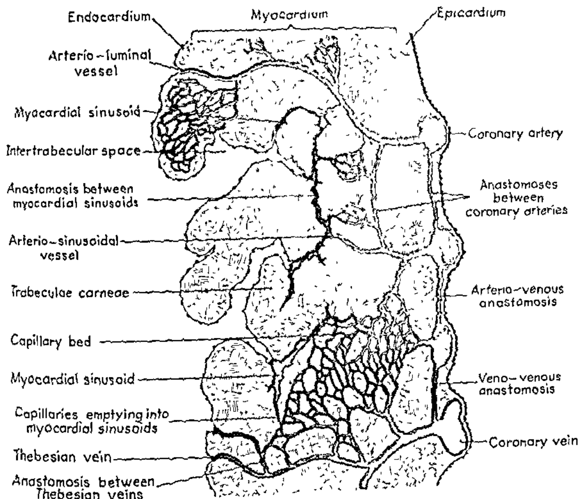


Figure III-18 Diagram of the ventricular wall, showing the relationship between the various intramural vascular channels

sulci of the ventricles. These trunks unite and course in the coronary sulcus to the region of the root of the pulmonary trunk. Thence they pass along the dorsal aspect of this trunk and leave the *pericardial* cavity to empty into one of the bronchial lymph nodes, and join the lymphatic drainage system of the mediastinum

THE FIBROUS FRAMEWORK OF THE HEART

The Annuli Fibrosi. In the adult heart the *myocardium* of the atria is nearly completely separated from that of the ventricles by a fibrous framework or "skeleton" which gives attachment to the atrial and ventricular musculature. The fibrous framework or fibrous base of the heart is formed essentially by four rings of densely woven collagenous fibers which surround the two atrioventricular ostia, the root of the aorta, and the root of the pulmonary trunk. These rings are called the *annuli fibrosi*. They reinforce the attachment of the valves of these orifices (Figures III-21 and III-22). The *pulmonary annulus* is attached to the *aortic annulus* by a heavy band of fibers called the *conus ligament* (Figure III-19).

The Fibrous Triangles. The fibrous framework is most massive in the space

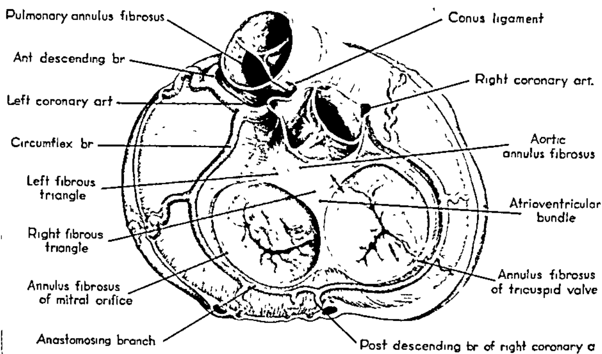


Figure III-19 Ventricular portion of the heart viewed from above with the atria removed, to show the fibrous triangles, the annuli fibrosi and the attachment of the ventricular musculature to them The fatty epicardium has been removed from the atrioventricular sulcus in order to show the coronary arteries

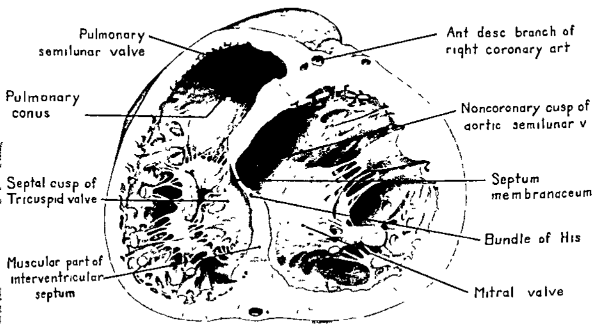


Figure III-20 Interior of the ventricular base of the heart, exposed by removal of the apical half of the ventricles The interventricular septum has been partially cut away to show the relations of the interventricular septum membranaceum, the mitral, the tricuspid, and the aortic semilunar valves

which is bounded by the right and left atrioventricular annuli and the aortic annulus. This area is called the *right fibrous triangle* or *trigone* (Figure III-19) The *left fibrous triangle*, smaller than the right, lies in the angle between the left aortic ring and the left atrioventricular ostium. It is this dense tissue of the region of the right fibrous triangle that with increasing age may acquire an almost cartilaginous character, reminiscent of the cartilage and bone that develop in the same region of the hearts of some of the ungulates. Through this right fibrous triangle passes the only connection between the atrial and ventricular myocardium, the *atrioventricular bundle* or *bundle of His.*

It will be recalled that there is a thin fibrous portion of the interventricular septum known as the septum membranaceum (Figures III-11, III-20 and III-22) The heavy collagenous fibers which are interwoven to form the septum membranaceum are continued into the ventricular face of the right fibrous triangle This union is so intimate that the septum membranaceum is sometimes described as a part of the fibrous framework of the heart.

THE HISTOLOGY OF THE HEART

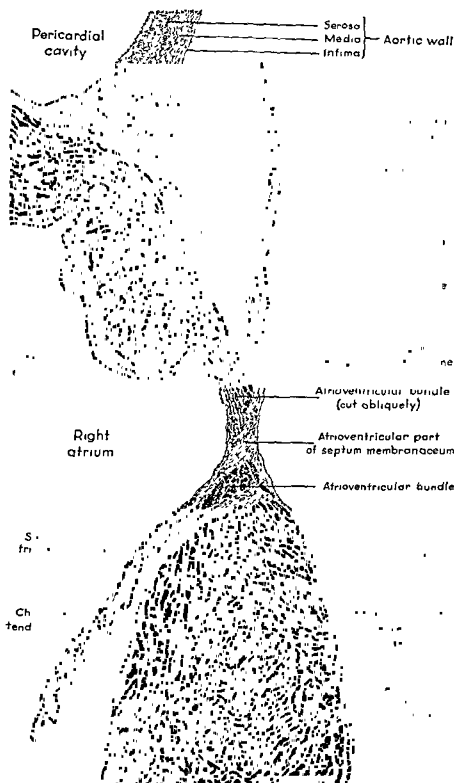
The Endocardium. All the cavities of the heart are lined with a simple squamous epithelium, called endothelium. This delicate lining is supported by a layer of fibroelastic connective tissue The endothelium and its subjacent connective tissue make up the endocardium. The connective tissue of the endocardium tends to be differentiated into a subendothelial layer of delicate collagenous fibers and a deeper layer with abundant elastic fibers. In it are found a few blood and lymph capillaries, and a rudimentary layer of smooth muscle fibers. The endocardium of the atria is markedly thicker than that of the ventricles and usually contains somewhat more smooth muscle although, even in the atria, the amount of smooth muscle is so small as to be of questionable functional significance. In the region of the base of the heart the endocardial connective tissue is continuous with the fibrous framework (Figure III-21).

The Myocardium. The myocardium of the heart wall consists of cardiac muscle and its supporting connective tissue. The fibers of the atrial myocardium are attached to the annuli surrounding the two atrioventricular ostia (Figures III-21 and III-22) The more superficial of these fibers either encircle both atria or enter the interatrial septum to form a figure-eight pattern about both atrial cavities The deeper fibers are attached to only one annulus and encircle one atrium only

The ventricular myocardium is complex in arrangement It consists of interwoven bundles and bands of muscle fibers which are partially separated from each other by fibroelastic connective tissue, and distinguishable by their orientation (Robb and Robb, 1942). In general, the fiber-bands of the layer nearest the endocardium have a course almost at right angles to that of the most superficial fiber-bundles of the same area (Figure III-23). The intervening fiber-bundles exhibit all degrees of intermediate obliquity All of these bands of cardiac muscle arise from, and insert into, the fibrous framework of the heart. Their attachment for the most part is directly into the fibrous base of the heart Certain fiber-bundles, however, may attach to the fibrous skeleton of the heart indirectly by means of the chordae tendineae and atrioventricular valves. The cardiac muscle fibers are invested by layer of delicate reticular and collage



Figure III-21 Projection drawing (X 8) of a section through the dorsolateral wall of an adult human heart. The section passes through the coronary sulcus and shows the left atrial wall above and the left ventricular wall below the dorsal (posterior) leaflet of the mitral valve (cf. Figures III-5 and III-19). The section was taken far enough dorsally to pass through the coronary sinus rather than the great cardiac vein (cf. Figure III-16).



... drawing (X 8) of a section through the interventricular sep-
The section was taken at such an angle
he noncoronary cusp of the aortic valve
e atrioventricular bundle lying at the
transition from the membranous to the muscula the interventricular septum

fibers which make up the *endomysium.* The groups of muscle fibers are partially set apart from adjacent bundles by more dense layers of fibroelastic connective tissue, called the *perimysium* This perimysial connective tissue is continuous with the endomysium, and its fibers blend with those of the endocardium and the epicardium to weld the heart wall into a coherent unit. It is in the perimysium and the endomysium that one finds the network of blood and lymph capillaries and the myocardial sinusoids which have been described (Figure III-18). In routine preparations, most of the smaller blood channels of the myocardium are not filled with blood. It is, therefore, difficult to appreciate the extraordinary richness of the finer vessels unless special efforts have been made to inject them before fixation

The individual muscle fibers are branched and anastomose to such a degree (Figure III-27) that it is meaningless, either morphologically or physiologically, to attempt to state their length Their diameter varies, that of fibers of the typical ventricular myocardium averaging about 12 micra in fixed material The surface layer of the fiber is a delicate membrane called the *sarcolemma* which is in immediate contact with the endomysium. Within the sarcolemma is the *sarcoplasm* serving as a matrix for *myofibrils* These myofibrils are coarse and give the cardiac muscle fibers a longitudinally fibrillated appearance. The myofibrils tend to clump together in fixed material so that in cross section the muscle fibers tend to show a cart-wheel pattern. The myofibrils are not optically homogeneous, but exhibit dark (anisotropic) and light (isotropic) areas along their length. These areas tend to line up across the diameter of the fiber, giving it a cross-striated appearance. There are also thin bands, particularly well stained with iron hematoxylin, which run across the muscle fibers, either straight or in a step-wise manner. These are the *intercalated discs* Their functional significance is still uncertain, although the consensus at present is that they do not represent boundaries between individual cells, and that the cardiac muscle fibers, therefore, form a true syncytium.

The conduction system of the heart is formed from cardiac muscle fibers which differ somewhat in their detailed structure from the "typical" muscle described above. The histology of these fibers will be considered later, after the course of the conduction system has been discussed.

The Epicardium. The face of the heart wall which abuts on the pericardial cavity is covered by mesothelium, a simple squamous or cuboidal epithelium. This, with a subjacent layer of fibro-elastic connective tissue, constitutes the epicardium (visceral pericardium). The connective tissue of the epicardium contains a considerable amount of fat, particularly in the region of the sulci and around the larger vascular channels which lie over the surface of the ventricles. It is continuous with the connective tissue forming the serosa of the great vessels entering and leaving the heart. The deeper layer of the epicardial connective tissue is continuous with the perimysium of the myocardium, except where it blends with the dense fibrous tissue of the annuli fibrosi (Figure III-21). In regions where there is no mesothelial layer, such as between the reflections of the pericardium (Figure III-6), the epicardial connective tissue is continuous with that of the mediastinum.

The Valves of the Heart. All the valves of the heart have essentially the same basic structure. They consist of a fold of endocardial connective tissue covered by endothelium. The connective tissue is differentiated into two main layers, one associated with each face of the valve. As a convenience in describing valves of the

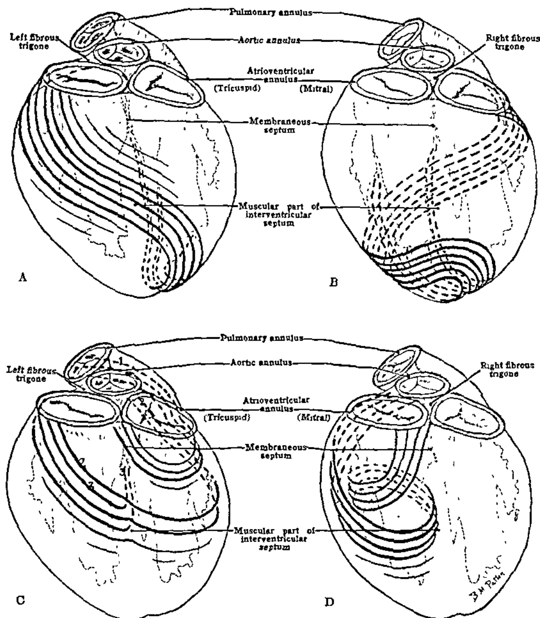


Figure III-23 Diagrams illustrating schematically the courses followed by some of the major groups of ventricular muscle-fibers (Based on the work of MacCallum, and Tandler, and on dissections by Alexander Barry From Morris' *Human Anatomy*, courtesy of The Blakiston Company, Philadelphia.)

The background of each diagram is a posterior view of the heart drawn as a semitransparent object The directions followed by the muscle fibers are indicated by red lines, which are solid on the side toward the observer and broken on the side away from the observer, or where they lie deep in the interventricular septum A Fibers starting superficially from the [illegible] and ending in the [illegible] to the deeper layers of both ventricles, [illegible], fibers partly within the deeper layers of the ventricular walls but terminating in the septum D. Fibers passing through the septum and making a double spiral in the walls of the left ventricle.

type encountered in the cardiovascular system, they may be said to have a "holding face" and a "deformed face." The term "holding face" is used to designate the face of a valve against which pressure builds up when the valve is closed. The fibers which predominate in the connective tissue layer of the holding face are coarse collagenous bundles which afford the maximum strength. Since the denseness of the collagenous lamina makes the holding face relatively incompressible, the opposite face of the valve must be stretched as the valve opens and closes. It is, for this reason, called the deformed face. The connective tissue of the deformed face of a valve has fewer and smaller collagenous fiber bundles and a conspicuous proportion of interwoven elastic fibers. In the case of the atrioventricular valves the holding face is toward the ventricular cavity, and into the dense white fibrous layer constituting it are inserted the collagenous fibers of the chordae tendineae The endothelial covering of these chordae is continuous with that covering the ventricular surface of the valve (Figures III-21 and III-22). The fibrous layers of the valve are continuous with the fibrous framework of the heart The continuity of the fibers of the holding face is particularly intimate, giving the valve a strong attachment. There may be small amounts of atrial muscle projecting for a short distance into the base of the atrioventricular valves.

The holding face of the semilunar valves is toward the lumen of the aorta or the pulmonary trunk. These valves have no chordae tendineae, and depend for their strength on the intimate fusion of their densely-woven laminae with the annuli fibrosi (Figure III-22).

The atrioventricular valves from hearts of older persons often are quite richly vascularized (Bayne-Jones, 1917). However, since this vascularization is found most often in hearts of persons with a history of previous endocarditis, and since the valves from hearts of young healthy persons show but a few very small vessels, it seems probable that markedly vascularized atrioventricular valves are not to be considered normal, but are the result of previous pathologic change (Kugel and Gross, 1926); Wearn *et al.*, 1936, Koletsky, 1946).

THE SINOVENTRICULAR CONDUCTION SYSTEM

The embryonic myocardium possesses three fundamental properties: inherent rhythmicity, conductivity, and contractility. The myocardium of the adult heart has differentiated functionally along these three lines There is the tissue making up the nodes of the conduction system which is specialized along the lines of inherent rhythmicity. The muscle making up the bundle of His, its branches, and the so-called Purkinje fibers, is specialized for rapid conductivity. The "typical" muscle forming the greater part of the myocardium of the atria and the ventricles seems to have been specialized in contractility. In spite of their characteristic specialization in one property, all of these types of heart muscle possess all three of the above basic properties in some degree.

The histology of "typical" cardiac muscle has already been described. In contrast with it we may characterize the other types of myocardium as "atypical" since, although they possess the basic characteristics of cardiac muscle, these characteristics differ quantitatively and qualitatively from their counterparts in typical cardiac muscle. As will be shown later, the tissues considered as atypical cardiac muscle differ among themselves as to their microscopic structure. To a certain extent the atypical cardiac muscle of the conduction

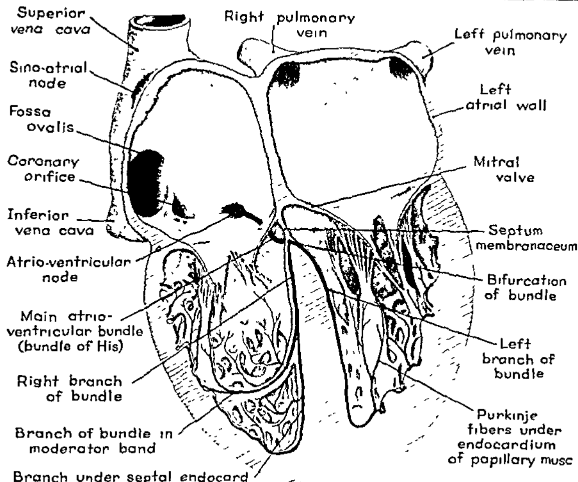


Figure III-24. Schematic diagram of heart opened frontally with the location and relations of the several parts of the sinoventricular conduction system indicated in red This figure should be compared with the less schematic views from the right (Figure III-25) and from the left (Figure III-26)

system shows some of the morphologic characteristics of embryonic myocardium It must be emphasized, however, that with this apparent structural simplicity is associated a high degree of physiologic specialization, as indicated, for example, by its high rate of impulse propagation.

The contraction of the heart is initiated in a mass of nodal tissue lying near the inlet of the superior vena cava. This is called the *sinoatrial node* (Figures III-24 and III-25) and is derived from a portion of the myocardium of the right horn of the sinus venosus of the embryonic heart On the basis of present evidence the excitatory impulse is believed to spread thence over the typical cardiac muscle of the atrium to a second mass of nodal tissue This is the *atrioventricular node,* lying in the floor of the right atrium When isolated experimentally it has a rate of inherent rhythmicity that is slower than that of the sinoatrial node, but higher than that of the myocardium in general In the intact heart it follows the pace of the faster pulsating sinoatrial node. From the atrioventricular node the impulse passes along the fibers of the *atrioventricular bundle* or *bundle of His,* which conducts ten times as rapidly as does the typical cardiac muscle of the ventricle (Wiggers, 1923). The bundle of His

pierces the fibrous base of the heart and normally forms the only myocardial connection between the atrium and the ventricle. At the crest of the muscular portion of the interventricular septum the bundle of His divides to pass to the right and left ventricles (Figure III-24). At the end of the ramifications of these branches they attain a different histologic character and are known as *Purkinje fibers.* These fibers are continuous with the typical cardiac muscle fibers, and pass the excitation wave on to them The entire complex of atypical cardiac muscle which is concerned with the propagation of cardiac contraction is known as the *sinoventricular conduction system.*

The Sinoatrial Node. As indicated in the preceding section the sinoatrial node lies in the wall of the right atrium in the region of the sulcus terminalis between the right atrium proper and the sinus venarum (Figures III-24 and III-25). It is roughly carrot-shaped and consists of a main mass in the deep part of the crista terminalis near the entrance of the superior vena cava, with a prolongation coursing at least 2 cm. caudally along the sulcus terminalis It is supplied by a strikingly constant small branch of the right coronary artery which reaches the sulcus terminalis by passing through the notch between the superior vena cava and the right auricular appendage (Figure III-14) This artery is a useful landmark in locating the sinoatrial node since it lies embedded along the axis of the nodal tissue Some workers have reported cephalic extensions of nodal tissue that partially surround the dorsal and lateral aspects of the orifice of the superior vena cava.

Histologically the atypical cardiac muscle which makes up the sinoatrial node consists of delicate fibers varying between 2 and 7 micra in diameter, loosely interwoven into a snarl of anastomosing strands (Figure III-27). These fibers are less strongly cross-striated than are those of the typical myocardium, and they possess fewer myofibrils. They can be seen to be continuous with the typical myocardial fibers of the adjacent atrial wall, and the transition between the two is so gradual that no sharp line of demarcation can be established.

Atrioventricular Node. A second mass of similar nodal tissue is found in the floor of the right atrium, to the left of the coronary sinus and adjacent to the base of the interatrial septum immediately above the right fibrous triangle This is called the atrioventricular node (Figures III-22 and III-25). Except where they extend into the atrioventricular bundle its fibers are continuous with those of the atrial myocardium without definite line of demarcation The histologic structure of the atrioventricular node is essentially that of the sinoatrial node, except that the former is more compactly arranged and the fibers are slightly thicker, ranging from 3 to 11 micra in diameter.

The Atrioventricular Bundle. At one point on its inferior margin the fibers of the atrioventricular node gradually become aligned and emerge from the node to form a single fascicle known as the atrioventricular bundle (bundle of His). This bundle pierces the right fibrous triangle (Figure III-19), courses along the caudal edge of the septum membranaceum (Figure III-25), and thus comes to lie along the apical edge of the muscular portion of the interventricular septum (Figures III-11 and III-22). This bundle of atypical myocardial fibers is somewhat isolated from adjacent cardiac muscle fibers by an investment of connective tissue According to Mahaim (1931) and Davies and Blair (1935), the fibers of the atrioventricular bundle have essentially the same histologic characteristics as those which form the atrioventricular node (Figure III-27), except that they are arranged

Ascending aorta
Superior vena cava
Pulmonary cone
Right coronary artery
Right branch of atrioventricular bundle
Atrioventricular bundle
Atrioventricular node
Anterior papillary muscle
Fossa ovalis
Septal cusp of tricuspid valve
Valve of coronary sinus
Inferior vena cava

Figure III-25 Simplified diagram of the heart opened from the right as in Figure III-8, to show the location of the sinoventricular conduction system Where this tissue lies subendocardially it is shown in solid black, where it lies deep within the myocardium it is indicated by broken lines

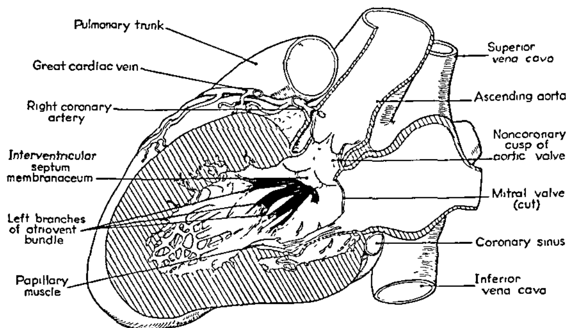


Figure III-26 Simplified diagram of the heart opened from the left as in Figure III-10 *The solid black indicates the position of the left branches of the atrioventricular bundle (of His).*









Figure III-27 Drawings (X 600) showing the characteristic histology of various parts of the sinoventricular conduction system

A Sinoatrial node (partly after Blair and Davies, 1935) A portion of the wall of the small artery that characteristically lies in the nodal tissue is included, lower left Note the slender strands of nodal muscle in its adventitia

B Atrioventricular node (partly after Blair and Davies, 1935). Note the strikingly irregular arrangement of the myofibrils at some of the points of fiber branching This is suggestive of conditions seen in early stages of histogenesis of cardiac muscle (Cf Figure II-6, B)

C. Typical ventricular muscle drawn to the same scale for comparison.

D Fibers of the so-called Purkinje type. These are found in their most characteristic form in the terminal ramifications of the conduction bundles close under the ventricular endocardium. Where Purkinje fibers diverge from the edges of a branch their direct continuity with typical ventricular muscle may frequently be seen (upper right).

more nearly parallel. In some persons, however, there may be found, in this bundle, fibers of considerably greater diameter which strikingly resemble the Purkinje fibers typically found more distally in the conduction system.

The Left Branches of the Atrioventricular Bundle. At the apical edge of the septum membranaceum, the bundle of His *is usually described as dividing into two* branches which distribute to the right and the left ventricles This division, however, is not dichotomous (Kistin, 1949) The left branch might better be described as a broad sheet of fascicles that sweep down over the left side of the interventricular septum, immediately beneath the endocardium, to reach the papillary muscles and lateral walls of that ventricle (Figure III-26) According to Mahaim (1931), the first of these fascicles of the "left branch" may leave the bundle of His within a few millimeters of the atrioventricular node The fibers making up the left branches of the bundle of His are about 18 micra in diameter. They have, to a certain extent, the characteristics described by Purkinje (1845) for some of the fibers in the subendocardial layer of the ventricles of ungulate hearts and, therefore, are called Purkinje fibers Since they are rich in sarcoplasm they stain lightly. They contain relatively few myofibrils and are weakly cross-striated The intercalated discs are readily recognizable and between them the fibers tend to bulge so that they have a somewhat bloated appearance (Figure III-27). They usually contain more glycogen than do the typical cardiac muscle fibers, although this cannot be demonstrated unless the autopsy material is exceptionally fresh

For the sake of clarity, the use of the designation "Purkinje fiber" should be confined to this particular type of large, pale fiber. Much of the confusion that has arisen in discussions of the sinoventricular conduction system has been caused by the indiscriminate use of the term "Purkinje tissue" to describe other parts of the sinoventricular conduction system to which it it not applicable either historically or histologically For similar reasons the term "Purkinje system" should not be used to designate the *sinoventricular conduction* system as a whole.

The Purkinje fibers may be seen to spread in fascicles over the subendocardial surface of the ventricle It is not difficult to trace Purkinje fibers directly over into fibers of the typical ventricular myocardium It seems reasonable that this direct continuity is the typical method of connection between the sinoventricular conduction system and the ventricular myocardium

The Right Branch of the Atrioventricular Bundle. The right branch is usually described as single, although some instances have been reported of an accessory fascicle leaving the bundle of His to distribute fibers along the more caudal side of the interventricular septum Ordinarily the main right branch follows the general course of the bundle of His It may even be described as a continuation of that bundle after it has given off the last fascicle to the left For descriptive purposes the right branch of the atrioventricular bundle may be divided roughly into thirds Its proximal third courses superficially, directly beneath the endocardium, to the region of the crista supraventricularis where it loses its superficial position and plunges deep within the myocardium The middle third may be regarded as beginning at this point and ending where the branch regains its subendocardial position (Figure III-25) Its distal third is entirely superficial in position and fans out as branches to the anterior papillary muscle and to the rest of the right ventricular wall When the moderat band is present, one of these fasciel

conduction tissue from the right branch lies within it (Truex and Copenhaver, 1947). Small fascicles from the bundle of His as well as from its two branches supply the musculature of the interventricular septum.

The fibers making up the proximal third of the right branch of the atrioventricular bundle usually have the same histologic characteristics as those making up the bundle itself The middle third, which lies deep within the myocardium of the interventricular septum (Figure III-25), is very small in diameter and its fibers are so similar to those of the adjacent cardiac muscle that it is next to impossible to identify it by its histologic character alone When, in its distal third, the right branch regains its subendocardial position, it branches into broad fascicles whose fibers have characteristics which justify calling them Purkinje fibers.

INNERVATION OF THE HEART

The heart receives a dual innervation from the sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions of the autonomic nervous system The preganglionic neurons of the sympathetic division are situated in the upper four or five thoracic levels of the spinal cord These synapse with second-order neurons which lie in the ganglia of the sympathetic trunks (White, 1936) The precise termination of the postganglionic fibers on the heart is not definitely understood.

The preganglionic neurons of the parasympathetic nervous system lie in the dorsal efferent nucleus of the medulla Their fibers pass as branches of the vagus nerve to the heart wall, where they synapse with the second order neurons. The latter collectively constitute a diffuse terminal ganglion. The gross arrangement of the sympathetic (postganglionic) nerves and the parasympathetic (preganglionic) nerves to the heart is shown in Figure III-28.

The superior and middle cervical ganglia give off, respectively, the *superior* and *middle cardiac nerves,* while the *inferior cardiac nerve* arises from the inferior cervical and perhaps the first thoracic ganglion. These cardiac nerves descend to the region of the ascending aorta and aortic arch, around which they anastomose to form the *cardiac plexus* Each vagus nerve contributes to the cardiac plexus by way of the *superior* and *inferior cervical nerves* and a *thoracic cardiac branch,* the latter usually arising from the recurrent laryngeal nerve

The cardiac plexus may be divided for descriptive purposes into a superficial and a deep portion The *superficial cardiac plexus* is spread over the ventro-caudal surface of the aortic arch. It is formed chiefly by the inferior cervical cardiac branch of the left vagus nerve, and the left superior cardiac nerve of the sympathetic system. The small *cardiac ganglion* (of Wrisberg) when present, is associated with this plexus It lies between the aortic arch and the pulmonary trunk to the right of the ligamentum arteriosum (Figure III-28).

The *deep cardiac plexus* lies dorsal to the arch of the aorta between it and the bifurcation of the trachea. It is formed by the three sympathetic cardiac nerves on the right, the three cardiac branches of the right vagus, the superior cervical and the thoracic cardiac branches of the left vagus nerve, the middle and inferior cardiac nerves of the sympathetic trunk, and direct branches from the first five or six thoracic sympathetic ganglia

There are extensions of the cardiac plexus over the atria, especially in the

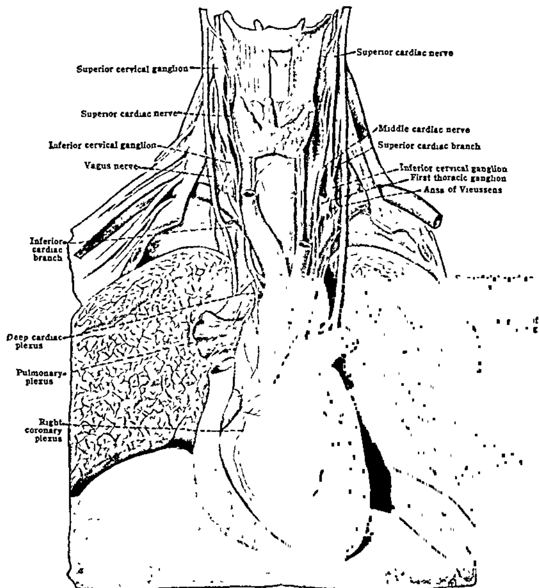


Figure III-28 Ventral view of dissection to show the nerve supply to the heart (After Tandler, from Morris' *Human Anatomy*, courtesy of Julius Springer and The Blakiston Company)

region of the sinoatrial node. Ramifications from it also are present in the atrioventricular sulcus, extending along the course of the right and left coronary arteries to form the *right* and *left coronary plexuses.* Scattered among these nerve fibers are ganglion cells which are considered to constitute the diffuse terminal ganglion of the vagus nerve.

The nodes and bundles of the sinoventricular conduction system are accompanied by numerous nerve fibers. However, the present consensus is that the function of the autonomic nervous system, with regard to the heart muscle, is regulatory. Insofar as they affect the heart rate, the sympathetic fibers accelerate, and the parasympathetic fibers slow the inherent rate of rhythmicity.

There are afferent nerve fibers passing from the heart to the central nervous system, passing back along the course of the branches of the vagus and sympathetic already described, with the exception of the superior cardiac nerves of the sympathetic division (Hirsch and Orme, 1947).

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CHAPTER IV

Physiology of the Heart

A. Normal Cardiac Physiology

HAROLD D. GREEN

This work was supported by grants from the National Heart Institute, Federal Security Agency, and United States Public Health Service.

I. INITIATION AND CONDUCTION OF THE CARDIAC IMPULSE

The Specialized Tissue for Initiation and Conduction of Cardiac Impulse

Myocardium. The atria and ventricles are composed of cardiac muscle which is made up of an anastomosing dense meshwork of multinucleated cross-striated and longitudinally-fibrillated fibers. The fibers in the walls of the right atrium anastomose with those of the interatrial septum and of the left atrium Similarly, there is abundant anastomosis of fibers of the two ventricles and of the ventricles with those of the interventricular septum. However, except as noted below, there is normally no muscular connection between the atria and the ventricles.

Sinoatrial and Atrioventricular Nodes and Conduction Tissue. At the right anterior junction of the superior vena cava and right atrium the myocardial fibers become gradually modified in structure, and closely associated with nerve fibers and cells, to form the *sinoatrial node* (S-A node) (Keith and Flack, 1907). Similarly, at the junction of the right atrium with the ventricles, near the coronary sinus and adjacent atrial septum, the atrial muscle fibers again become gradually modified in structure, and associated with large numbers of nerve cells and fibers, to form the *atrioventricular node* (A-V node) (Tawara, 1905, 1906, Kisten, 1949).

Specialized Conduction Tissue. The fibers of the A-V node pass through into the upper fibrous interventricular septum as a common bundle (His, 1893) which then divides and spreads out over the endocardial surface of both sides of the interventricular septum to form the specialized conduction system of the ventricles (Purkinje, 1845). These modified myocardial conduction fibers anastomose directly with the subendocardial muscle fibers of the lateral walls of both ventricles and also penetrate through the ventricular walls, anastomosing with the myocardial fibers of all layers (Abramson and Margolin, 1935-36)

Accessory muscle fibers connecting the atria and ventricles have occasionally been described (Wood *et al.*, 1943), they may be the same as those described by Kent in 1893 (Erlanger, 1943). They are probably responsible for the electrocardiographic syndrome of the short P-R interval with prolonged QRS complex (Wolff, Parkinson and White, 1930, Feil *et al.*, 1947)

Glomset and associates (1940a, 1940b, 1945) find large numbers of nerve cells and fibers present in the S-A and A-V nodes and in the region normally considered to contain conduction tissue, they have been unable to demonstrate the presence of modified muscle fibers in these regions. On the basis of these observations, they conclude that "nerve fibers may play a large part in the genesis and conduction of the nerve impulse" All other recent investigators, however, sustain the above-described muscular nature of the nodes and conduction system (Nonidez, 1943, Davies and Francis, 1946, Truex and Copenhaver, 1947).

The "Pacemaker"

Site of the Primary "Pacemaker." It is apparent from inspection of the exposed beating heart that, in the mammal, the cardiac impulse originates in the atria and after a brief pause spreads to the ventricles, whereas in the amphibian (turtle), the impulse originates in the sinus near its junction with the atrial canal and then spreads by way of the atrial canal to the atria, and subsequently to the ventricle. The exact site of origin of the heart beat is less obvious but has been determined,

various experimental procedures. McWilliam (1888) observed that application of cold to the right atrium of mammalian hearts at the site of the S-A node caused slowing of the heart rate and that heat similarly applied caused speeding, whereas such applications elsewhere had no effect on the heart rate. This has repeatedly been confirmed by subsequent investigators (Schlomovitz and Chase, 1916). When a galvanometer was connected to a pair of exploratory leads placed successively upon various pairs of points on the surface of the atrium, the earliest evidence of electrical negativity in the heart cycle was always at the electrode closest to the site of the S-A node (Wybauw, 1911, Lewis *et al*, 1910-11, Eyster and Meek, 1913-14; Meek and Eyster, 1916; Eccles and Hoff, 1934)

Premature beats at various points on the atria have been electrically induced during the recording of a standard electrocardiogram A premature beat was considered to have been induced at or near the site of the normal pacemaker when the electrical record of the premature beat most nearly approximated that of a normal beat and when the premature beat was followed by a normal beat at a normal interval. By this procedure the "normal pacemaker" was also located at the site of the sinoatrial node (Lewis, 1910-11). The site of the pacemaker has also been determined by observing the effects of destruction of various parts of the atrium (Gotch, 1909-10, Jourdan *et al.*, 1945). Borman (1926) found that all of the S-A region had to be destroyed before the cardiac impulse would arise elsewhere. Paff (1936) observed that the sinus tissue of chick embryo, when transplanted to the region of the pulmonary conus, retained its dominant rhythm, and that as soon as anastomoses developed between the myocardium of the conus and the transplanted sinus tissue, the two began to beat synchronously, the beat spreading from the conus region toward the rest of the ventricle.

From the above observations it is evident that the cardiac impulse normally arises from the region of specialized tissue lying in the right atrium at its junction with the superior vena cava. Since by similar experiments the impulse has been shown to arise in the sinus at is junction with the atrium in the turtle heart (Eyster and Meek, 1913-14; Meek and Eyster, 1916, Schlomovitz and Chase, 1916), and since it is generally assumed that the modified myocardial tissue found at the site of origin of the impulse in mammals is analogous to the sinus tissue in the turtle, the site of the pacemaker in the former is designated the sinoatrial node

Secondary "Pacemakers." When, for any reason, the S-A node is depressed, one of several regions of lower excitability may serve as the pacemaker. In order of descending excitability, these are the atrioventricular node (A-V node), the atrioventricular bundle above the bifurcation of the conduction system, the atrial tissue, the branches of the atrioventricular bundle, and the ventricular musculature (Lewis *et al.*, 1913-14, Meakins, 1913-14; Meek and Eyster, 1913-14).

The cardiac rate, with the sinoatrial node as pacemaker, may vary from 45 to 170. The inherent cardiac rate with impulse initiation in the atrioventricular node or the common bundle, *i e.*, nodal or supraventricular rhythm, is 30 to 60 (usually 35 to 50) per minute. When the pacemaker is located in the ventricle (presumably in one of the bundle branches) the inherent rate is usually of the order of 20 to 30 per minute (Katz, 1946). (See also Table IV-1, page 186).

Mechanism of Action of the "Pacemaker." The inherent mechanism for the rhythmic discharge of impulses from the sinoatrial node is still a subject for speculation It may represent a rhythmic build-

up and breakdown in the potential of a membrane The build-up of potential of a membrane probably is brought about by a pumplike mechanism in the cell membrane which increases the concentration of negative charges on the inside and of positive charges on the outside of the membrane. When the resulting difference in concentration (electrical potential) exceeds a critical value, the resistance of the membrane breaks down and the charges redistribute themselves in such manner as to reduce the potential across the membrane to, or nearly to, zero. According to such an analogy, the breakdown of the potential of the membrane would be the factor which initiates the cardiac impulse

Such rhythmic activity resembles that of a thyratron condenser circuit in which a condenser charge (and plate potential) are gradually built up until they exceed a critical value determined by the grid potential, at which moment the condenser discharges itself through the thyratron tube (Bozler, 1943). The frequency with which the impulse is generated could, according to this theory, be determined by the rate of build-up of the potential of the membrane, which would probably be a function of the cell metabolism, or it could be determined by any factor which regulated the potential difference at which the breakdown would occur. Either a slower rate of build-up of membrane-potential or a higher critical breakdown of potential would slow the frequency with which the cardiac impulse is generated.

Conduction of Cardiac Impulse

Conduction in the Atrium. Within the mammalian atrium, no special conduction path exists. The cardiac impulse spreads centripetally at the rate of 60 to 120 cm. per second (Lewis and co-workers, 1914), allowing the wave of electrical negativity to reach the right atrial appendage (right auricle) approximately 0.03 second, the left atrial appendage 0 045-0 06 second and the A-V node 0 02-0 045 second, after the initiation of the impulse in the S-A node (Bachmann, 1916, Eyster and Meek, 1913-14, 1941, Wiggers, 1949, p. 519). A specialized conduction path between S-A and A-V nodes is thought to exist in the rapidly-beating avian hearts (Davies and Francis, 1946).

Conduction in the Atrioventricular Node (A-V node). Precise measurements of the rate of conduction through the A-V node are not available because of the inaccessibility of the node It may be assumed that the impulse is conducted slowly, requiring at least 0 05 second (Gilson, 1942) The cardiac impulse passes readily from atrium toward ventricle, but normally it passes in the reverse direction with difficulty, if at all.

Conduction in the Ventricular Specialized Conduction Tissue. Beyond the A-V node the cardiac impulse is conducted at the rate of approximately 400 cm. per second by the common bundle and the left and right branches of the specialized conduction system (Lewis and Rothschild, 1915), so that all portions of the ventricle are excited within 0.04-0.08 second. The upper portion of the interventricular septum becomes excited first The ventral portion of the heart adjacent to the septum, two-thirds of the way from base to apex is excited next The impulse then spreads to the apex and the ventral portion of the right ventricle, and then to most of the surface of the left ventricle The last regions to be excited are the basal surface of the right and then that of the left ventricle. The lapse of time between the excitation of the first and last portions of the external ventricular surfaces is 0 025-0.045 second (Lewis and Rothschild, 1915; Robb and Robb, 1936, Abramson and Jochim, 1937; Wiggers, 1937; Eyster and Meek, 1941; Harris, 1941). In mam-

malian hearts the right side of the base in the region of the pulmonary conus may be the last region to be excited (Harris, 1941).

Conduction in the Ventricular Musculature. Robb and Robb (1936) claimed that the impulse spreads in the ventricle in the direction of the muscle fibers in the muscular sheaths which run parallel to the surface They recorded the sequence of local electrical activity from the potentials between an electrode on the body and each of a series of electrodes sewn on the surface of the heart. They claimed that, when the muscle bundles were cut between two of the surface points lying along the direction of the superficial fibers, local action-potentials disappeared at the more basal of two surface points. However, sewing the electrodes to the heart caused a partial injury depolarization, and cutting of the muscle caused development of a complete injury depolarization at the basal point so that it was impossible for them to have recorded whether or not activity had arrived at the basal point. Their evidence for conduction along muscle bundles is, therefore, inconclusive Furthermore, Lewis and Rothschild (1915) and Abramson and Jochim (1937) have shown there is no preferential spread of excitation along muscle bundles as compared with that at right angles to the superficial fibers. The latter authors believe that such spread of impulse as does occur in the ventricular myocardium is at a rate of only 30 to 50 cm. per second.

In isolated perfused hearts in which necrotizing substances were introduced into the empty left ventricular cavity, registration of epicardial and endocardial potentials, (the other electrode being a diffuse electrode) gave records which suggest that pathways exist for the rapid spread of ventricular excitation in portions of the wall apart from the tissues immediately beneath the endocardium (Pruitt *et al*, 1951). The speed of this spread appeared to be greatest in a direction parallel to the long axis of the fibers when isolated segments of the ventricular wall were studied.

Myocardial Units. Robb and associates (1948) have proposed that the ventricular myocardium is not a continuous syncytium, but that the myocardial fibers are arranged in small groups, each supplied by its own special conduction (Purkinje) fiber. The myocardial fibers of one group are separated from those of another by fibrous sheaths. These groups of myocardial fibers and associated special conduction fibers are thus analogous to the skeletal muscle nerve-motor units in which one nerve fiber supplies 50 to 150 skeletal muscle fibers. This would help to explain the observations of Lewis and Rothschild (1915) regarding the slow spread of premature ventricular beats over short distances, where the spread is principally through ordinary myocardial fibers as compared with the more rapid spread to greater distances in which the impulse probably spreads to the special conduction tissue and through it to more distant myocardial units.

Mechanism of Conduction. Conduction of the impulse in the heart, like that of nerve, is commonly considered to be a wavelike propagated membrane-depolarization in which the breakdown in potential difference at one region of the membrane initiates a depolarization or breakdown of potential in the next adjacent region The rate of propagation of the impulse is dependent on the properties inherent in each portion of the tissue through which the impulse is travelling. Following depolarization, a period elapses during which the membrane will not respond to an impulse or other form of stimulus. This interval is designated the *absolute refractory period.* A relative refractory period then follows during which the membrane

will respond, but only to a stronger than normal stimulus. The absolute and relative refractory periods are the intervals during which the membrane is restoring its membrane-potential difference. Excitability returns to normal as the membrane-potential is restored to its normal value. Occasionally a phase of excessive polarization, a supernormal phase, then ensues, during which the membrane may be excited more readily than normal. It is believed that the supernormal phase does not occur normally, but that it may be seen in the depressed heart (Katz, 1946). Nahum and Hoff (1939) suggest that the U wave of the electrocardiogram represents the supernormal phase; the majority of premature ventricular beats fall on the part of the cycle where the U wave occurs. The recovery of membrane-potential, *i.e.*, the phenomenon occurring during the refractory periods, is not a wave phenomenon or conducted impulse like the wave of depolarization, the rate of recovery of membrane-potential and of excitability is dependent on the local metabolic activity at each point. Changes in the rate of recovery, and inversely, therefore, of the duration of the refractory period, frequently parallel changes in the velocity of propagation of the impulse but the two are probably not causally related. During the relative refractory period, conduction is slower than normal. When the refractory period becomes longer than the interval between the two cardiac impulses, the second of the two impulses dies out as it reaches an area which is still refractory, producing a form of heart block (see page 182).

Ventricular Excitability

The "All or None Law." When a ventricle is excited artificially with an adequate stimulus on the external or internal surface, the impulse spreads over the entire ventricle. A longer time usually lapses, however, between the application of the stimulus and the excitation of the last part of the ventricle, than in the case of the normal mode of excitation, because of the longer path involved (see page 178). If a quiescent ventricle is excited with a series of such single stimuli which are progressively increased in strength and spaced not closer than one per second, no response will be recorded until a certain intensity is reached – the threshold stimulus – in response to which the ventricle will contract. Further increase in intensity of stimulus will not, however, increase the strength of the response. The ventricle, therefore, responds maximally or not at all to a given stimulus. In this regard and despite its multinucleated, multifibrillated structure, it behaves like a single skeletal muscle fiber rather than a skeletal muscle composed of many fibers.

Refractory Period of the Ventricle. Like the conduction tissue noted above, the ventricular myocardium becomes completely refractory upon responding to a stimulus, and remains so until about the beginning or shortly after the start of relaxation. A relative refractory period then follows in which excitability gradually returns to normal. It is thus impossible to induce a state of complete tetanus in cardiac muscle even with rapid, adequate stimuli. However, with rapid repetition, some of the stimuli will fall in the "vulnerable" period of a previous contraction, *i.e.*, early in diastole, and may start a continuously moving impulse which keeps travelling about the ventricle immediately after the preceding response and thus establishes the state known as ventricular fibrillation (see page 181). The refractory period shortens with increase in heart rate and lengthens with slowing and with strengthening of the heart beat. The refractory period tends to be shortest in

muscle and longest in the nodal tissue (Katz, 1946). Variations in refractory period, particularly of nodal tissue, play a part in the genesis of certain arrhythmias (see Part B on Abnormal Cardiac Function).

2. CARDIAC CYCLE

Pressure and Volume Curves

An understanding of the events in the cardiac cycle has been derived from simultaneously recorded cardiac volume and pulmonary trunk, aortic, intra-atrial and intraventricular pressure curves (Figure IV-1)

Methods for Cannulating the Cardiac Chambers. Pressure curves were first recorded from cannulae inserted into the cardiac chambers through their walls in animals with opened thorax. More recently pressures have been recorded from the right atrium and ventricle and the pulmonary trunk in man by passing catheters, measuring 125 cm in length, into these chambers by way of the antecubital vein and the superior vena cava under fluoroscopic guidance (Cournand *et al*, 1944, Richards, Jr., 1946; Sosman, 1947; Dexter, 1947) Numerous catheterizations have now been performed with relatively few complications, but it should be remembered that some trauma to endothelium and myocardium may result even from the most careful procedure (Banfield *et al*, 1950). Pressures have also been recorded from the human left ventricle by a catheter passed toward the heart by way of a carotid artery and then retrograde through the aortic valve (Zimmerman *et al.*, 1950) and by direct transthoracic ventricular puncture (Buchbinder and Katz, 1949) "Pulmonary capillary pressure," or probably more correctly, a pressure which closely approximates left atrial pressure has been recorded by passing a catheter *via* the right atrium, right ventricle, and pulmonary trunk until it becomes lodged in a small branch of one of the pulmonary arteries (Gorlin and Haynes, 1950; Hellems *et al.*, 1948).

Atrial pressure can be estimated by a manometer connected to a needle inserted into an antecubital vein only when the subject is supine and all portions of the vein between the needle and the heart are below the heart level. With the subject sitting, the internal pressure in the vein as it passes over the upper portion of the thoracic cage is less than atmospheric pressure and the vein therefore collapses. The needle is thus no longer connected by a continuous fluid column with the heart and cannot correctly record atrial pressure. This was demonstrated by Davis and Shock (1949) who found the venous pressure to increase as the subject shifted from the supine to the sitting position, whereas intra-atrial pressure decreased, when recorded by a noncollapsible catheter passed into the atrium

Pressure Manometers. Various forms of pressure manometers have been attached to the above-mentioned cannulae and catheters for making a permanent record of the pressures at each instant in the heart cycles The types most commonly used at the present are all membrane manometers In the case of the optical manometers, flexing of the membrane causes a light beam, reflected from a mirror attached to the membrane, to move transversely across a strip of photographic paper which is moving vertically. In the direct-writing type of pressure manometers the membrane is attached to a resistance or capacitance unit in such manner that the resistance or capacitance varies with the degree of flexing of the membrane. The

fluctuations in resistance or capacitance are amplified and then fed into some form of recorder, such as the ink-writing oscillographs or those that write by passing a heated stylus over plastic-coated paper In the latter the paper turns black wherever the stylus touches it. (For details of pressure manometers and recording technics, see Motley *et al*, 1947; Ellis *et al.*, 1950; Green, 1950a, and Lambert, 1950) A minute manometer which can be inserted directly into the cardiac chambers has been devised by Ellis, Gauer and Wood (1951). This manometer is attached to the tip of a cardiac catheter and has the same caliber as the latter. It gives more faithful reproduction of intravascular pressures than is possible with the manometers described above.

Standard Zero Reference Plane for Pressure Measurements. The numerical value obtained from pressure measurements in the cardiovascular system depends, of course, upon the horizontal plane to which zero pressure is referred Most commonly this has reference to the assumed level of the center of the atrium Stead and associates (1945) place this plane 5 cm. posterior to the fourth costochondral junction with the subject supine. McMichael and Sharpey-Schafer (1944) used the posterior surface of the thorax. Holt (1940) determined the level of saline meniscus with the subject prone, then supine, and placed the reference plane halfway between the levels assumed by the menisci in the two positions Lyons and associates (1938), Davis and Shock (1949), Battro and co-workers (1949), Dexter and associates (1950) and Green (1950b) placed the reference plane 10 cm anterior to the skin of the back with the subject supine This last reference plane appears to be the one most generally used and I shall, therefore, refer to it hereafter as the *standard zero reference plane*

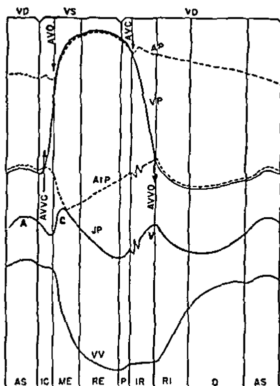


Figure IV-1 Relationship between aortic pressure *AP*, intraventricular pressure *VP*, atrial pressure *AtP*, jugular volume diastole, isometric reduced ejection, *P*, protodiastole, *IR*, isometric relaxation, *RI*, rapid inflow, *D*, diastasis *AVVC*, atrioventricular valve closes, *AVO*, aortic valve opens, *AVC*, aortic valve closes, *AVVO*, atrioventricular valve opens *A*, atrial (pressystolic) wave, *C*, carotid (systolic) wave, *V*, ventricular (diastolic) wave These curves are schematic and have been exaggerated, particularly the atrial pressure curve, in order to accentuate the various deflections (Reproduced from *Medical Physics*, Green, 1950)

Ventricular Pressure and Volume Curves. The events described in this paragraph are applicable to both the left and right chambers of the heart The curves to illustrate these events, Figure IV-1, are drawn as for the left ventricle. The events in the two chambers usually occur simultaneously, but those in the left chamber frequently precede those in the right. The difference in timing in man may range from minus 50 to plus 30 milliseconds (average 0) (Hamilton *et al.*, 1947). Atri

systole (AS) starts with the spread of excitation over the two atria. Owing to the time required for the spread of the impulse, the entire atrium is not excited simultaneously but contraction is semiperistaltic. As a result, as shown in Figure IV-1, the pressure in the atrium (AtP) rises relatively gradually and may even begin to decline before the end of the atrial systole. During atrial systole, the leaves of the atrioventricular valves float together and are partially closed by the rapid stream of blood induced by the atrial contraction. This facilitates the complete closure of the atrioventricular valves with the onset of ventricular systole, if ventricular systole begins just at the peak of atrial systole. If ventricular systole is delayed, as by a prolonged A_s-V_s interval, the atrioventricular valves may float apart again before ventricular systole occurs. As soon as the cardiac impulse reaches the ventricular musculature, ventricular systole begins Within 0 01 to 0 02 second, the rise in pressure in the ventricle (Figure IV-1, *VP*) forces the atrioventricular valves shut, giving rise to a series of vibrations of the cardiac structures which are audible through the stethoscope and which are designated the first heart sound. During the ensuing 0.02 to 0 04 second, the pressure within the ventricle continues to rise and the ventricular cavity becomes more rounded, but no change in the volume of the ventricle occurs (VV). When the intraventricular pressure exceeds the pressure in the aorta, the aortic valve is forced open and blood begins to be ejected into the aorta. The interval from the onset of ventricular systole to the opening of the aortic valve and pulmonic valve (AVO) is called the period of isometric contraction (IC). As indicated by the ventricular volume curve, blood is ejected rapidly at first, then more slowly. Ejection ceases when the ventricular muscle starts to relax. This marks the end of ventricular systole and the beginning of ventricular diastole. During the next few hundreds of a second, the protodiastolic phase (P), the blood starts to flow back from the aorta into the ventricle, causing aortic valvular closure (AVC). Vibrations induced by the snapping shut of this valve give rise to the second heart sound. All openings to the ventricular cavities then remain closed for about 0 08 second, the isometric relaxation (IR) phase, during which the tension in the ventricular muscle gradually disappears and the ventricle reassumes a more elongated shape but no change in ventricular volume occurs. When the pressure within the ventricular cavity drops below that in the atrium, the leaves of the atrioventricular valve are forced open and blood flows rapidly from atrium to ventricle. This initial rapid flow is produced by the elastic recoil of the atrium, the latter having been distended by the blood returning to it during the period of ventricular systole when the atrioventricular valve was closed. After a few hundredths of a second, however, the rate of inflow diminishes and thereafter corresponds more or less with the rate of return of blood to the heart by way of the veins. This interval of reduced flow is called diastasis. Atrial systole then begins, starting a new cardiac cycle (Wiggers, 1916-17, 1949; Green, 1950b).

The pressure in the left ventricle oscillates between 5 mm. of mercury diastolic and 90 to 140 mm. of mercury systolic in the course of the normal heart cycle. The pressure in the right ventricle in normal man varies between 19 and 27 mm. of mercury systolic and − 0 5 and + 6 mm. of mercury diastolic with reference to atmospheric pressure at the *standard zero reference plane* (see above) (Battro *et al*, 1949, Richards, 1949; Dexter *et al.*, 1950).

Atrial Pressure. During atrial systole the atrial pressure rises, reaches a maximum, and then falls while some parts of

the atrium are still contracting (Figure IV-1, *AtP*). With the beginning of ventricular isometric contraction, the atrial pressure falls rapidly because of the downward pull of the ventricle as it is rounded by contraction. The drop in pressure continues during rapid ventricular ejection because of the decreasing intrathoracic pressure which results from reduction in the size of the ventricle and ejection of blood from the thoracic cavity (Blair and Wedd, 1945-46). About the middle of ventricular systole, the atrial pressure starts to rise, reaching a maximum at the instant when the atrioventricular valve opens; the pressure then drops as the atrium, by its elastic recoil, empties itself into the ventricle. During the remainder of diastole, atrial and ventricular pressures rise slightly as the ventricle becomes distended with blood returning to the heart

The pressures in the right atrium oscillate with respiration between − 7 and + 16 mm of mercury measured relative to atmospheric pressure and with reference to the *standard zero reference plane* (see above) with the subject supine The left atrial pressure is closely approximated by measurement of *"pulmonary capillary pressure"* (see above). The normal value for "pulmonary capillary pressure" is 5 to 12 mm of mercury averaging 6 to 9 mm of mercury (Hellems *et al*, 1948, Richards, 1949, Dexter *et al*, 1950) By simultaneous measurement of pulmonary capillary pressure and cardiac output, Gorlin and Haynes (1950) believe they can accurately estimate the cross-sectional area of the mitral valve For these estimates they assume left atrial pressure to be 5 mm of mercury with reference to the *standard zero reference plane* with the subject supine.

Jugular Venous Pressure. Jugular venous pressure (Figure IV-1, *JP*) is practically identical with atrial pressure except for the presence of a sharp rise in pressure, corresponding with the onset of ventricular ejection, which is produced by the impact of the underlying carotid artery as it expands with the rising aortic pressure. Three waves are thus normally present in the jugular venous pulse: the A wave corresponding with atrial systole, often called the P or presystolic wave, the C wave corresponding to the impact of the carotid artery, also called the S or systolic wave, and the V (ventricular) or D (diastolic) wave. The rising phase of the V wave is produced by distension of the atrium and jugular vein as blood returns to the atrium but is unable to enter the ventricle while the atrioventricular valves are closed, and the descending limb is produced by the rapid collapse of the atrium and jugular vein as blood flows from them into the ventricle during the phase of rapid filling of ventricular diastole. As will be described later, the A (P) wave is absent in atrial fibrillation. Since the triple wave which is present with the normal heart may be readily seen, the presence of a double, instead of a triple, wave makes it possible to diagnose atrial fibrillation clinically. The amplitude of the A wave is increased during augmented venous return and decreased during diminished venous return (Mackay, 1947)

Pressure in Aorta and Pulmonary Trunk. As the result of the ejection of blood into the aorta in an intermittent stream, the pressure in the central aorta pulsates with each heart cycle (Figure IV-1, *AP*). During ventricular ejection, blood enters the aorta faster than it can flow out through the capillaries, and the pressure rises rapidly during the initial phase of systole, and more slowly as ejection slows. The aortic pressure begins to drop rapidly during protodiastole, rebounds abruptly immediately following closure of the aortic valve and then again declines steadily during ventricular diastole as blood flows out of the aorta through the capillaries. The notch corre-

sponding to the closure of the aortic valve is called the incisura, the bottom of the notch marking the moment when the aortic valve closes. A slower wave of rising and falling pressure, frequently recorded following the incisura, is caused by the reflection from distant bifurcations of the wave generated by the preceding ventricular ejection A second slower wave may, with slow heart rates, be noted just before the next systole. This wave may be a reflection of the dicrotic wave from the periphery Waves of still higher frequency may be superimposed on the systolic phase of the aortic pressure curve, produced by reflections of the peripherally propagated initial pressure rise from nearby arterial bifurcations. A few vibrations or a slight rise in the aortic pressure may be seen during the isometric contraction of the ventricle, just before the systolic rise in aortic pressure These are produced in part by outward bulging of the aortic valve and probably in part also by some backflow of blood into the aorta from the coronary arteries during isometric contraction (see page 156) The pressure in the pulmonary trunk undergoes similar oscillations.

Methods for Obtaining Systemic Arterial Pressure. The precise pressure in the systemic arteries is best obtained by inserting a needle into an artery and connecting the needle with a suitable recording manometer For practical purposes the arterial pressure may be estimated with the clinical sphygmomanometer. The sphygmomanometer consists of a cuff, containing a rubber bladder to be placed around an extremity, a rubber bulb for inflating the bladder, and a manometer for measuring the pressure at which the bladder is inflated. When inflated to a pressure higher than the systolic arterial pressure no blood flows under the cuff At a pressure just below systolic pressure, a short pulse of blood flows under the cuff and gives rise to a sound (the first phase) which can be heard with a stethoscope placed over the artery just distal to the cuff. As the cuff pressure is lowered the sound becomes louder, thumping and roaring (second and third phases). At still lower cuff pressures the sound suddenly diminishes in intensity (fourth phase), then disappears entirely at a pressure about 5 to 10 mm. of mercury lower (fifth phase). Opinion is as yet divided as to whether the fourth or fifth phase should be taken as signaling the correct diastolic pressure. It is probably better to record both. To obtain reasonably satisfactory readings the subject should be seated, the cuff should be at least 12 cm wide for use on the adult arm (a wider cuff would be preferable for individuals with large fatty arms), the arms should be relaxed and slightly abducted (Stein, 1946).

Normal Values. The normal limits for the pressure in the brachial artery in young adults are 90 to 140 mm. of mercury systolic and 70 to 85 mm. of mercury diastolic (Wiggers, 1949) In a given individual the pulse pressure (systolic pressure minus diastolic pressure) closely parallels stroke volume output of the heart. According to Dublin and associates (1950), among persons in their twenties, systolic pressure ranges normally from 95 to 120 mm and diastolic pressure from 62 to 88. These values increase progressively with age, the increase in systolic pressure becoming more rapid about age 50, so that in the age group 60 to 64, normal systolic pressure ranges between 115 and 170 and diastolic pressure, between 70 and 100. Mortality from cardiovascular renal diseases increases rapidly with elevation of the arterial pressure above these normal levels.

The pressure in the pulmonary trunk varies normally between 19 and 27 mm of mercury, (average 23 mm. of mercury) systolic, and 6 and 12 mm. of mercury (average 9 mm. of mercury) diastolic (Hel-

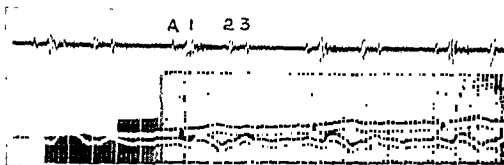


Figure IV-4 The principal heart sounds (upper curve), electrocardiogram (middle curve) and jugular pulse (lower curve) 1, indicates first heart sound, 2, second heart sound, 3, third heart sound, A, atrial or fourth heart sound (Reproduced from Scherbs, 1946)

ginning of isometric contraction (Dock 1945). Contributory factors may be the sudden development of tension in the ventricular muscle and the chordae tendineae (Orias, 1949). The sound caused by closure of the mitral valve is heard best at the point of apical impact, usually in the fifth interspace in the midclavicular line The sound from the closure of the tricuspid valve is heard best in the sixth interspace just to the right of the sternum When recorded, the first sound persists into the early ejection period; such a sound is probably generated by the early high velocity of blood flow and the resulting eddy currents in the blood stream When recorded the first heart sound is composed of five to 12 vibrations at frequencies of 33 to 111 cycles per second. There may be progressive increase in amplitude, progressive decrease, or there may be two peaks in amplitude suggesting a slight asynchrony in the closure of the two valves. The audible sound in the latter case may be described as split (Boyer *et al.*, 1940)

Second Heart Sound. The second heart sound produced by the closure of the aortic valve is heard best in the second right interspace; that produced by closure of the pulmonic valve, in the second left interspace. When recorded, a low frequency wave may be noted with the onset of protodiastole, this merges into a high frequency sound that is associated with the actual valve closure and is followed by further low frequency oscillations Three to eight vibrations may be present with frequencies of 33 to 111 cycles per second A split second sound may occur when the two semilunar valves close asynchronously (Orias, 1949)

Third Heart Sound. The third heart sound is associated with the rapid inrush of blood into the ventricle during the descending limb of the V wave of the jugular and atrial pressure curves. It has been considered to be more in the nature of a low-frequency murmur, corresponding to the murmur of mitral stenosis, than a sound in the sense of the first and second sounds The third heart sound is also believed to result from vibration of the ventricular walls because of sudden distension by the inrush of blood from the atria (Orias, 1949; Smith, 1944; Boyer, 1942) When recorded, it consists of one to three vibrations with frequencies of 33 to 50 cycles per second and is recordable in from 26 to 85 per cent of normal persons, depending on the sensitivity of the recorder to low-frequency vibrations Some cases of gallop rhythm are due to intensification of the third heart sound

Fourth Heart Sound. The fourth heart sound is associated with contraction of the atrium It has been recorded in 27 per cent of normal subjects. It also may be more like a murmur produced by rapid flow of blood through the atrioventricular valve than a sound caused by vibration of

cardiac structures. Other theories of its origin are that it is produced by the sudden distension of the ventricle or by a rebound closure of the atrioventricular valve following the rapid inflow accompanying atrial systole. Scherlis (1946) believes that the atrial sound has both components. The fourth heart sound, when recorded, usually consists of two to three vibrations with frequencies of 28 to 83 cycles per second. The fourth, or atrial, sound is most readily heard in persons with incomplete heart block or with idioventricular rhythm, when the atrium is beating at a faster rate than the ventricle. Under these conditions it may be recognized by its coincidence with the A wave in the jugular vein pulsation which accompanies atrial systole.

Factors Affecting Intensity of the Heart Sounds. The intensity of the first heart sound is related to the vigor of ventricular contraction, it is intensified with increased cardiac output or elevated aortic pressure and it is softened in instances of myocardial damage from any cause. The intensity of the first sound is also related to the interval between the atrial and ventricular systoles, in general, the longer this interval the louder the first sound. The intensity of the sound may thus be used as a rough measure of the interval between atrial and ventricular systoles (the P-Q interval in the electrocardiogram) (Levine, 1948, 1949, Levine and Harvey, 1949). During atrial fibrillation the first sound is louder after a short than after a long diastole, *i.e.*, when it occurs during the phase of rapid ventricular filling (Rytand, 1949) Two interpretations are offered to explain these phenomena. According to one view, atrial systole or rapid inflow into the ventricles causes the atrioventricular valves to become partially closed due to a "jet" effect; the final closing, like the unrolling of a rug, occurs almost immediately with the onset of ventricular systole and thus intensifies the sound. The other view, however, assumes that rapid flow from atria to ventricles pushes the valve leaflets apart and deep into the ventricles. With ventricular systole they then swing shut in a hinge-like fashion, giving a loud sound. If systole is delayed, the valves are assumed to float together prior to systole and the resulting closing sound with the onset of ventricular systole is weaker. Levine and Rytand both favor the latter explanation

The first sound is frequently intensified with tachycardia, emotional tension, hyperthyroidism, anemia, infections and fever (Levine and Harvey, 1949). A diagnostic sign of mitral stenosis is a loud snapping first sound Levine (1948, 1949) believes this is due to the abnormal position of the atrial valve leaflets in this disease, the leaflets lying deep in the ventricles, the papillary muscles being hypertrophied and the leaflets shortened. Alimurung and associates (1949) described eight cases in which the apical first sound was split or had a crescendo character which resembled the presystolic murmur of mitral stenosis.

The intensity of the second sound is related to the pressure in the appropriate vessel at the onset of isometric relaxation. Normally, the aortic second sound in adults is louder than the pulmonic but in instances of left heart failure or mitral stenosis, the reverse may be found. In instances of dilatation of the root of the aorta resulting from advancing age, the aortic second sound frequently has a tympanitic tone.

The second aortic sound is decreased in the presence of aortic stenosis (Levine and Harvey, 1949). The first and second sounds may be split or even duplicated, probably because of asynchronous onset or cessation of contraction in the two ventricles. This may be seen particularly in instances of bundle branch block or ventricular premature beats. The intensity of both the first and second sounds is louder

in thin-chested individuals and softer in thick-chested subjects.

The intensity of the various frequency components in the heart sounds has been analyzed by Foulger and associates (1947). A fairly large component of low frequency sounds was recorded. In general, increased intensity of cardiac work tended to augment the intensity of the higher frequency components in comparison with the low frequency vibrations.

Gallop Rhythm. Occasionally a third heart sound is heard which, by its timing, gives rise to a triple beating that resembles the hoof beats of a galloping horse. When the third sound occurs between the first and second sounds, it is called systolic gallop rhythm; when the third sound occurs between the second and first sounds, it is designated diastolic gallop rhythm. Systolic gallop rhythm is less common than diastolic gallop rhythm. It is generally loudest at the apex, usually with the patient recumbent. The exact cause of systolic gallop is not known; it is not believed to indicate a grave prognosis (Levine and Harvey, 1949). When heard loudest at the aortic area it may have originated as a result of impact of the aorta against other structures (Wolferth and Margolies, 1940).

As indicated above, sounds may be produced in diastole during the phase of rapid inflow into the ventricle which follows opening of the atrioventricular valves (early or protodiastolic gallop) and during the phase of rapid inflow that coincides with atrial systole (presystolic gallop). A loud third heart sound, probably produced by atrial systole, may be associated with marked prolongation of the A_s-V_s interval. If the heart rate is rapid enough, the protodiastolic and presystolic phases may practically coincide, giving a summated effect which may be more readily audible as a third heart sound and give rise to a mid-diastolic gallop rhythm (Braun-Menendez, 1938). Diastolic gallop is heard best at the apex and is encountered most frequently in hypertensive and coronary artery disease and less frequently in rheumatic valvular disease. It usually indicates serious derangement of the heart muscle (Levine and Harvey, 1949).

3. CARDIAC OUTPUT

Cardiac output may be defined as the volume of blood (in ml. or liters) ejected by one ventricle per minute. Under normal circumstances the output of the two ventricles per minute is the same and is, of course, equal to the volume of blood circulated through the body per minute. However, in aortic insufficiency, septal defects and patent ductus arteriosus, the output of the two ventricles differs from each other and from the volume circulated per minute. The cardiac output is, of course, the product of the heart rate times the average stroke volume (output per beat). Cardiac output is a function of the size of the individual. To allow for this, the output is usually expressed as the cardiac index, which is the output in liters per minute per square meter of body surface. Standard or basal cardiac output is measured under the same conditions as basal metabolism, *i.e.*, with the individual reclining, relaxed and in the post-absorptive state.

Methods for Measuring Cardiac Output in Man

Foreign Gas and Injection Technics. The earlier measurements of cardiac output in man were made with the foreign gas technics (Green, 1948a). The simplest technic was to have the subject rebreathe rapidly for a fixed interval of time from a bladder containing a known amount of the foreign gas. At the end of the rebreathing the volume (in ml.) of the

eign gas removed from the rebreathing bag was determined, and a sample of arterial blood was withdrawn and its content of the gas determined. Assuming that none of the foreign gas was present in the venous blood, the cardiac output (CO) would be:

$$\text{CO (in ml./min.)} = \frac{60 \times \text{ml. (gas absorbed)/(seconds for rebreathing)}}{\text{ml. gas/ml of arterial blood}}$$

The injection technic is similar in principle, the only difference being that the foreign substance is injected intravenously at a known constant rate (Hamilton, 1945, Hamilton and Remington, 1947b, Newman *et al*, 1950, Nylin and Celander, 1950).

Modified Foreign Gas Technic. Indirect Fick Principle. Since the rebreathing could alter the cardiac output, the foreign gas technic was modified in order to determine the average oxygen content of the venous blood. This latter figure, plus the figure for arterial oxygen content, and the rate of oxygen uptake per minute by the lung, measured by standard metabolic methods, gave the cardiac output (CO).

$$\text{CO (in ml./min.)} = \frac{\text{ml./min (oxygen uptake)}}{(\text{ml. } O_2\text{/ml. arterial blood}) - (\text{ml. } O_2\text{/ml. venous blood})}$$

The mixed venous oxygen content was determined by rebreathing a known mixture of oxygen and a foreign gas and simultaneously analyzing arterial samples for oxygen and the foreign gas content. From the foreign gas analyses the cardiac output during the rebreathing was computed, from this figure and the data on oxygen uptake and on arterial oxygen content during the rebreathing, the mixed venous oxygen content was computed. The foreign gas study was carried out immediately following the preceding oxygen measurements during natural breathing, and it was assumed that the average venous oxygen content did not change in the interval between the two sets of determinations (Grollman, 1932).

Error in Foreign Gas Technics. Both the above technics assume that the venous blood at no time contains any of the foreign gas. Unfortunately, recirculation always occurs, causing the actual arterial venous difference in foreign gas content to be smaller by about 24 per cent than is indicated by analysis of the arterial sample alone. The rebreathing also abnormally elevates the arterial oxygen content As a result, the cardiac output measured by this technic is always too low by about 33 per cent (Hamilton, 1945, Chapman *et al.*, 1950).

Ballistocardiograph. The ballistocardiograph records the oscillations in the longitudinal axis of the body produced by the caudal recoil of the heart as it ejects the blood cephalically, and the cephalic impact delivered to the body as the blood flows around the aortic arch and caudally The amplitude of these oscillations closely parallels the stroke volume output of the left ventricle (Starr, 1945, Nickerson, 1945)

Registration of Arterial Pulses. The stroke volume discharge of the left ventricle can also be estimated with fair accuracy by analysis of pressure tracings recorded from the systemic arteries (Hamilton and Remington, 1947a; Hamilton, 1950). This method has numerous limitations (Duomarco *et al.*, 1948).

Electrokymograph. Estimations of stroke volume output of the heart have been made from the pulsations recorded with the electrokymograph. They appear to agree favorably with cardiac output determined

simultaneously by the Stewart injection and the direct Fick principles (Ring *et al*, 1950a, b).

Quantitative Versus Relative Measurements of Cardiac Output. The ballistocardiograph, the registration of arterial pulses and the electrokymograph do not yield direct measures of cardiac output, but only relative changes. The actual output can be calculated only by applying a factor computed from simultaneous comparison with other more direct quantitative methods such as the direct Fick principle. The ballistocardiograph is also likely to give results having considerable error in the presence of tachycardia. These methods are, however, easy to employ and provide useful information, particularly of the relative changes in output from beat to beat in the same individual These methods, and particularly the last, give valuable additional information in dynamic disturbances such as coarctation of the aorta, valvular lesions and ventricular aneurysms

Direct Fick Principle. The introduction of the technic for passing a catheter into the right atrium and ventricle (see page 132) allowed direct sampling of the mixed venous blood This method has now become the standard for measurement of cardiac output. Simultaneous observations are made of the mixed venous and of arterial blood oxygen content and of the rate of oxygen uptake by the lungs. The cardiac output (CO) is calculated as follows:

$$\text{CO (in ml /min.)} = \frac{\text{ml /min (oxygen uptake)}}{(\text{ml. } O_2/\text{ml. arterial blood}) - (\text{ml. } O_2/\text{ml. venous blood})}$$

Potential errors are those due to anxiety in the patient because of insertion of the catheter and those resulting from failure to obtain a true mixed venous sample. If the catheter is in the superior vena cava the sample will be too high in oxygen content, and if near the coronary sinus the sample will be too low in oxygen content. The most accurate samples are obtained from the right ventricle or pulmonary trunk (Cournand, 1945; Cournand *et al*, 1945; Warren *et al.*, 1946; Warren, 1948). When properly performed this method has a high degree of accuracy (Seely *et al.*, 1950).

Normal Values. Measurements of cardiac output made principally with gasometric rebreathing technics, and with the ballistocardiograph, calibrated upon the basis of the earlier gasometric technics, indicate that under basal conditions the cardiac output in the adult is 2.96 to 4.61 liters per minute and that the cardiac index is 2 2 ± 0 3 liters per minute per square meter (Grollman, 1932, Chapman *et al*, 1950). Practically all of the more recent observations, however, using the standard technic of catheterization of the right atrium or ventricle, give higher cardiac indices [2.12 to 4 01 (ave. 3.12) l /min /M², Cournand *et al.*, 1945; 2.3 to 4 1 (ave 3 35) l /min./M², Stead *et al*, 1945; 1 88 to 4 62 (ave. 3.27) l /min /M², Chapman *et al*, 1950, and 2 8 to 5 0 (ave. 4.2) l./min /M², Dexter *et al*, 1950]. In view of the many errors inherent in the earlier gasometric methods, it seems likely that the figure of 3 3 ± 1 l./min./M², obtained by the catheterization technic, is more nearly correct, especially since the index obtained by this method compares favorably with the indices obtained in experimental animals. The cardiac output per beat, using the latter technic, ranges from 53 to 108 with an average of 84 ml. per beat. It should be emphasized that normal figures can be obtained only when the subject is in a basal state, as in testing for basal metabolism, *i e.*, in a postabsorptive state, after a night's rest, without having exerted himself for at least one-half hour prior to the test, having ı

fever, and being free from anxiety and emotional tension.

Cardiac Output Under Various Physiologic Conditions

Conditions in Which Output is Unchanged. The cardiac output is apparently the same when the person is asleep as when he is awake and in the horizontal position It is also unaffected by smoking, by menstruation, or by moderate variations in external temperature although it may be increased 5 to 30 per cent at environmental temperatures above 30 C, or by low temperatures if accompanied by shivering

Increased Output. Cardiac output may be increased 50 to 100 per cent by anxiety and 30 to 40 per cent by eating. The response to eating is diphasic, there is an initial increase during eating with a return to normal, and then a delayed increase during digestion. Pregnancy (Hamilton, 1949), fever, anemias with a hemoglobin level of less than 7 6 grams, hyperthyroidism, arteriovenous fistulas, acidosis, and low oxygen tension in inspired air, i e, below 10 volumes per cent at atmospheric pressure, are conditions which increase cardiac output as much as 100 per cent. In maximum exercise, the oxygen consumption may be increased twelve-fold and the cardiac output as much as nine-fold Under these conditions, the heart rates may be increased three-fold and the remaining three-fold increase is caused by an increase in stroke volume. The cardiac output is increased by vasodilator drugs, by epinephrine, by atropine (McMichael and Sharpey-Schafer, 1944) and, in certain types of heart failure, by digitalis. Cardiac output is also increased with rapid intravenous infusion.

Decreased Output. The cardiac output is decreased 25 to 33 per cent in changing from the recumbent to the vertical position (McMichael and Sharpey-Schafer, 1944). Sudden tachycardias of 200 or more per minute, or marked bradycardia such as is present in heart block, reduce the cardiac output (Katz *et al.*, 1945b). The output is also reduced during inhalation of 100 per cent oxygen (Whitehorn *et al*, 1946) in myxedema, constrictive pericarditis, shock, following myocardial infarction and in many forms of heart failure. In the last, the output may not be abnormally reduced at rest but may not increase to the extent seen in normal persons during exercise. For further discussion of this subject, see pages 216, 235 and 236.

Regulation of Cardiac Output. The wide fluctuation in cardiac output under the various conditions noted above indicates that various factors must be present to bring about the required changes in cardiac output Such variations are necessary since the rate of oxygen consumption in severe exertion may be increased twelve-fold whereas only a three-fold increase in oxygen supply could be provided by removing all the oxygen from the blood ordinarily flowing through the tissues, *i.e*, by increasing the oxygen utilization from 30 to 100 per cent. In general, in normal subjects, the cardiac output is closely regulated to the need for oxygen, so that the arteriovenous difference in oxygen content rises only slightly above the normal value despite large increases in oxygen utilization by the body

A. INTRINSIC CARDIAC MECHANISMS

The intrinsic behavior of cardiac muscle has been studied in the heart-lung preparation Under these conditions, humoral and nerve influences are abolished and it is possible to alter one factor at a time while keeping the other factors constant. With this preparation, the effect of the central venous pressure, of heart rate and of aortic pressure have been carefully studied (Star-

ling and Visscher, 1926-27). These findings have been largely corroborated by catheterization studies in man.

Effect of Initial Length or Tension of Ventricle. The volume of blood in the right ventricle at the end of diastole is probably of the order of 130 ml. and at the end of systole, 50 ml. The corresponding volumes in the left ventricle are presumably similar (Richards, 1949). When the arterial pressure and heart rate are kept constant, increasing the systemic central venous pressure produces a progressive increase in cardiac output per beat up to five-fold (McMichael and Sharpey-Schafer, 1944 Ring *et al.*, 1949). With small initial increases in tension, the initial volume of the ventricle increases quite rapidly With each increment in initial tension (or length) the vigor of ventricular systole increases, ejection becomes more abrupt and the volume ejected becomes larger * Despite the greater stroke volume, the volume of blood retained by the ventricle at the end of systole may increase progressively, in other words, the ventricle may empty itself less and less completely, with each increase in venous pressure In the above experiment, the myocardial oxygen consumption increases proportionately to the initial length; the increase, however, is less than the increase in stroke volume so that the efficiency of ventricular contraction, that is, the ratio of cardiac work to myocardial oxygen consumption, decreases.

With the heart excised from the pericardium, and with excessive elevations of venous pressure, a degree of initial tension and length is attained at which the heart is no longer able to increase further its stroke volume of ejection With still greater increase in venous pressure, the heart may then reach a state of decompensation in which the cardiac output per beat may be progressively reduced despite a further increase in oxygen consumption. It is thought, however, that in the normal heart, the rigidity of the pericardium prevents such an extreme degree of overdistention

Measurements of the normal human ventricular cavities indicate a normal capacity of approximately 140 ml. for each chamber Since the normal stroke volume is approximately 84 ml., whereas with severe exercise the stroke volume increases to around 240 ml, it is apparent that under normal conditions the ventricle is not completely filled. Also, it probably never completely empties itself The latter is confirmed by recent roentgenologic studies with Diodrast Nylin (1943) estimates that the residual blood in the whole heart at the end of systole is 400 ml when recumbent and 200 ml when erect Gernandt and Nylin (1946) find a close correlation between circulation time and systolic residual volume.

Effect of Heart Rate. Increase in heart rate curtails both systole and diastole but preponderantly the latter and, therefore, results in reduction in the time for ventricular filling. If the heart-lung preparation is adjusted so that a constant venous return is maintained, then acceleration of the heart rate temporarily produces a slight increase of cardiac output but very shortly a new condition of equilibrium is established in which the cardiac output is the same as it was before cardiac acceleration. This is so because, under such conditions, the central venous pressure is decreased and this plus the decrease in diastolic filling time results in a smaller initial ventricular tension and length and, therefore, in a decrease in stroke volume Under these conditions, the cardiac oxygen-consumption increases with the heart rate and, since there is no increase in output per minute, the cardiac efficiency is decrea

* Di Palma and Reiss (1948) conclude, from myographic studies, that the vigor of contraction decreases with increased diastolic size

If the perfusion system is adjusted to maintain a constant central venous pressure during cardiac acceleration, the stroke volume remains almost constant and, as a consequence, the cardiac output is increased almost in proportion to the heart rate. Under these conditions and within certain limits of acceleration, the decreasing diastolic time has a minimal influence on the ventricular filling. Ventricular volume curves suggest that the failure of the shortening of diastolic time to reduce cardiac filling is due to a more rapid relaxation of the ventricle early in diastole, which thus allows it to receive blood from the atrium more rapidly. Augmentation of cardiac output per minute by acceleration of the heart rate requires a greater increase in myocardial oxygen consumption than that needed in a similar augmentation in output produced by increasing the stroke volume. In normal man cardiac acceleration produced by atropine is accompanied by an increase in cardiac output per minute and a decrease in right atrial pressure (Kelly and Bayliss, 1949). In the intact dog the stroke volume is related inversely to the heart rate The optimum heart rate for maximum output per minute is 130 Above 180 beats per minute, cardiac output declines rapidly (Remington, 1950).

Effect of Aortic Pressure. Elevation of aortic pressure leads to a momentary reduction in stroke volume and, therefore, to a slight systolic residue; this residue added to the normal volume of diastolic inflow leads to greater initial length and to a restoration of the stroke volume to normal, at which time the cardiac output per minute also returns to normal. Under these conditions, however, the ventricle is constantly operating at a greater initial diastolic length and with a resulting greater oxygen consumption and a slightly higher left atrial pressure (Katz *et al.*, 1945b).

Effect of Pressure in Pulmonary Trunk. Increase of the pressure in the pulmonary arterial circuit affects the right ventricle in a manner analogous to that of elevation of aortic pressure upon the left ventricle. The right ventricular initial volume and tension increase and right atrial pressure rises (Katz *et al.*, 1945b).

Independence of the Two Ventricles. The above data indicate that the two ventricles are independent of each other in their response to work load. In recent experiments the right ventricular contractility was completely destroyed by cauterization without causing significant change in either right atrial or pulmonary arterial pressures (Bakos, 1950). The author concludes that an actively functioning right ventricle is not absolutely necessary for the maintenance of a normal pressure gradient in the pulmonary arterial tree since the left ventricle can apparently transmit part of its energy through the continuity of the circumscribing individual ventricular muscle bands.

Effect of Inherent Contractility. Changes in inherent contractility may also affect the cardiac output and the initial length of the ventricular fibers even when the venous and aortic pressures remain constant (Green, 1948b). This phenomenon is designated as a change in "tone" in the ventricle by Johnson and Katz (1937). For further discussion see page 152 in section on Nervous and Humoral Regulation of Heart.

B. EXTRINSIC MECHANICAL FACTORS AFFECTING CENTRAL VENOUS PRESSURE AND CARDIAC OUTPUT

Certain mechanical factors extrinsic to the heart modify cardiac output principally by their influence on the volume of blood and on the pressure within the central systemic venous reservoir and the pulmonary venous and left atrial reservoir, respectively.

Normal Values for Central Systemic Venous Pressure. The value for central sys-

temic venous pressure depends, of course, upon the horizontal plane to which zero pressure is referred. Most commonly this has reference to the assumed level of the center of the atrium, *i.e.*, the *standard zero reference plane* (see page 133). Normal values with this reference plane are 5 to 15 cm. of saline.

Blood Volume and Distribution of Blood. This pressure is immediately determined by the volume of blood within the central venous reservoir, *i.e.*, within the superior vena cava, the inferior vena cava above the diaphragm and right atrium, and by the distensibility of this part of the venous system. The quantity of blood within this reservoir is, in turn, dependent upon the *total blood volume and upon the capacity of the total vascular system.* The portions of the system, the capacity of which can be varied, include the cardiac chambers themselves, the pulmonary vascular bed, the systemic arteries, the systemic capillaries and the peripheral systemic veins and such special blood vascular beds as the spleen, the splanchnic viscera and the liver (Ralston *et al.*, 1945-46; Green, 1950b).

Cardiac Output. Under ordinary conditions, a rise in central venous pressure induces an increased filling and, therefore, an increased output of the right ventricle which in turn increases the output of the left ventricle. However, the output of the heart may increase in spite of a decrease in venous pressure during cardiac acceleration or when myocardial contractility is increased (Katz *et al.*, 1945b, Kelly and Bayliss, 1949). Other factors remaining constant, an increase in the cardiac output removes blood from the venous side of the circuit and increases the quantity of blood and the pressure in the arterial and capillary portions of the circuit; and conversely, a decrease in the cardiac output per minute decreases the total quantity in the arterial and capillary circuit and increases that in the entire venous system, including the central systemic and pulmonic venous reservoirs. With cessation of cardiac output, such as occurs with ventricular fibrillation or cardiac standstill, the arterial and capillary pressures drop progressively and the venous pressures rise until the pressures throughout the cardiovascular system become equalized. Under experimental conditions the systemic venous pressure may rise as much as 3 to 10 mm. of mercury during the establishment of this equilibrium (Green, 1950b).

Changes in Vascular Capacity. Central venous pressure appears also to be altered as a result of active changes in the caliber of the entire vascular system. The rise in systemic venous pressure after the exercise probably represents a decrease in the volume of blood pooled in certain portions of the vascular bed owing to an active decrease in their size. This displaced blood, accumulates in the central venous reservoir, raising the pressure there. Active changes in vascular capacity probably also occur in anemia with marked reduction in the blood volume, with little or no decline in central systemic venous pressure, and in other conditions, such as after injection of epinephrine (Connet, 1920-21), during anoxia, after acute hemorrhage, in traumatic shock (Silfverskiold, 1946) and possibly in heart failure (see page 241). The spleen, liver, venous plexi and the veins may all participate in the changes of vascular capacity. McMichael (1949) calls particular attention to the importance of venomotor tone which he believes is controlled by the sympathetic nervous system under the regulation of a center in the nervous system which is closely associated with the vasomotor system regulating arteriolar vasoconstriction. He believes venomotor reflexes are brought into play when there is a need for increased cerebra

circulation, and that conversely a dilation of the veins and fall in venous pressure results when the pressure in the carotid artery is high and presumably when, therefore, cerebral circulation is adequate.

Posture. The decreased cardiac output (see page 144) on changing from the reclining to the vertical posture probably results principally from pooling of blood in the more dependent parts of the body, particularly in the veins This reduces the volume of blood available to fill and distend the central venous reservoirs and, therefore, results in a decreased stroke-volume output by the heart. This condition is aggravated by quiet standing in which the full hydrostatic pressure from the heart down to the lowest veins becomes manifest (Scott, 1936, Sweeney and Mayerson, 1937), and is considerably decreased by even mild exercise of the legs such as rocking back and forth from heel to toe. Such muscular activity rhythmically compresses the veins in the legs and, by virtue of the valves in the veins, pumps the blood toward the heart and thereby reduces the peripheral venous pressure and the quantity of blood which is stored in the dependent capillaries and veins The dependent pooling is aggravated by anything which increases the apparent weight of the blood, such as the centrifugal force in the pull-out of an airplane during a dive or sharp turn (Green, 1950b, Gagge and Shaw, 1950). Marked pooling of the blood is also occasionally seen in patients with severe varicose veins. In these patients and in patients with systemic edema from heart failure, a reverse phenomenon is seen not infrequently after resumption of the horizontal position. When the patient lies down, the veins in the legs are able to empty. As a result, the capillary pressure in the dependent portions is decreased and fluid is absorbed from the tissues, increasing the total blood volume; both of these changes serve to increase the volume of blood and the pressure within the central venous reservoir. These, in turn, increase the output of the right ventricle. If the left ventricle is unable to cope with this increase in the right ventricular output, a rise in left atrial and pulmonary venous and capillary pressures results which leads to pulmonary edema and dyspnea (cardiac "asthma"; see page 238).

Respiration. During normal inspiration the abdominal pressure increases and the intrathoracic pressure decreases. These changes favor return of blood to the systemic central venous reservoir and the filling of the right ventricle in diastole, increasing its output. However, simultaneously, the extravascular pressure on the pulmonary capillaries is decreased, thus increasing their capacity and delaying the transmission of the above effects to the left atrium and left ventricle. During expiration the reverse effects occur, decreasing the output of the right ventricle, but because of the decrease in the pulmonary capillary capacity, blood is forced into the left atrium from the lungs, increasing the output of the left ventricle However, if the respirations are slow enough, the decreased output of the left ventricle seen at the start of inspiration may be counterbalanced and may even increase as the elevated output of the right ventricle becomes transported through the lungs to affect the left atrial and left ventricular diastolic pressure (Lauson *et al.*, 1946, Seely, 1948).

During positive-pressure artificial respiration, the net filling pressure of the right ventricle is decreased during the rising-pressure phase of inspiration and increased during the decreasing-pressure phase of expiration. It is concluded that a minimal effect on average cardiac output is obtained with an intermittent positive-pres-

e breathing mask which develops a dual increase in mask-pressure during piration, a rapid drop in pressure at the l of inspiration, and a mean mask-pres- e during expiration as near atmospheric essure as possible (Cournand *et al*, 18).

Dogs, when breathing against a constant sitive pressure of 16 cm of saline, owed a decrease of cardiac output, an rease in central systemic venous pressure and a decrease in the gradient from peripheral to central veins When breathing against a constant negative pressure of 16 cm. of saline, the central venous pressure fell and the gradient from peripheral to central veins, increased, probably because of collapse of the veins as they entered the thorax while the cardiac output remained approximately normal (Holt, 1944).

4. WORK OF THE HEART

The mechanical work done by the heart r beat is roughly the product of the vol- ie of blood ejected per beat times the erage pressure against which the blood ejected, *i e*, the average or mean aortic essure during systole Although this thod gives a reasonably close approxi- tion, strictly speaking, the work should computed by dividing the period of tole into an infinite number of incre- nts of discharge, multiplying each in- ment by the aortic pressure during the rement, and summing all of the prod- s for the systole

The above method, based on aortic pres- e, measures only the pressure energy rk of the heart Some additional energy, wever, is required to give the blood its tial velocity. This velocity or kinetic ergy has been computed for the human rt by Prec and associates (1949) They culated that the kinetic energy for the rk of the left ventricle was 0 25 to 2 0 cent of the total, while the kinetic ergy for the right ventricle was 2.4 to 5 per cent of the total The higher per it for the right ventricle is due to the t that the kinetic energy work for the o ventricles is about the same, but average aortic pressure is four to five es that in the pulmonary trunk and refore the pressure energy work for the t ventricle is four to five times that for the right ventricle. The kinetic energy is converted back to pressure energy as the velocity of blood flow slows during diastole, therefore, it is possible that by multiplying the stroke volume discharge by the average aortic pressure throughout the heart cycle one may obtain a reasonably close approximation to the total work per beat The heart work per minute is of course the heart work per beat times the number of heart beats per minute

In discussing factors which affect the work of the heart many authors speak of pressure work and volume work Strictly speaking, there is no such thing as volume work, all work being a product of volume ejected times pressure against which it is ejected However, when the cardiac output is greatly increased without any significant increase in aortic pressure, it is permissible to say that the volume work has been greatly increased, and conversely, if the aortic pressure is greatly elevated with no change in cardiac output, one may say there has been an increase in pressure work As indicated on page 146, an increase in the volume work may be tolerated with less increased demand for oxygen by the myocardium than would be the case with a proportional increase in pressure work. Further investigation must be done in man on this aspect of cardi physiology.

5. NERVOUS AND HUMORAL REGULATION OF HEART

Nerve Supply

Sympathetic Fibers. Pre-ganglionic sympathetic fibers, capable of affecting the heart, leave the spinal cord by way of the upper five thoracic roots. The synapses are found in the corresponding paravertebral and the stellate ganglia and the postganglionic fibers then proceed to the heart by way of the cardiac nerves (Cannon *et al.*, 1926, Kuntz and Morehouse, 1930, Pannier, 1946, Saccomanno *et al*, 1947, Chapman *et al.*, 1948; Smithwick *et al.*, 1949). They are distributed to the S-A and A-V nodes, conduction tissue, atrial and ventricular musculature and coronary arteries (Nonidez, 1939). Since stimulation of the peripheral end of the cut vagus in the neck may cause an acceleration of the sympathectomized cat's heart, it has been concluded that a few sympathetic fibers reach the heart by way of the vagus (Brown and Maycock, 1942, Middleton *et al.*, 1949). However, this apparent sympathetic effect may be due to the acetylcholine released by the normal vagal endings (see page 152). The effect of sympathetic nerve stimulation is mediated by an epinephrine-like substance released at the sympathetic nerve terminals.

Parasympathetic Fibers. Parasympathetic pre-ganglionic fibers are conveyed to the heart in the vagi. The synapses with the postganglionic fibers are found in the intrinsic cardiac ganglia. Postganglionic fibers of parasympathetic origin are distributed to both the S-A and A-V nodes, to the upper portion of the special conduction tissue, to the atrial myocardial fibers and to the coronary blood vessels but none are known to be distributed to the ventricular myocardium (Garrey and Ashman, 1931; Nonidez, 1939). Parasympathetic nerve impulses are mediated to the tissues by acetylcholine released at the nerve terminals (Abdon, 1945).

Regulation of Heart Rate (Chronotropic Regulation)

Sympathetic nerve impulses cause the sinoatrial node to initiate cardiac beats more frequently; parasympathetic impulses conversely cause the sinoatrial node to initiate cardiac beats less frequently (Gilson, 1938). Evidence from experiments on dogs suggests that the right vagus and the right sympathetic nerves both contain more fibers affecting the S-A node than do the corresponding nerves of the left side (Pannier, 1946; Nonidez, 1939; Saccomanno *et al.*, 1947).

The manner in which sympathetic and parasympathetic impulses affect the sinoatrial node will remain in doubt until more precise knowledge is available concerning the inherent character of initiation of the impulse. However, it appears that epinephrine or an epinephrine-like substance released at the sympathetic endings and acetylcholine released at the parasympathetic endings are involved, since these substances are found in the perfusate leaving the heart after prolonged stimulation of the appropriate nerves, and since these substances, when added to the perfusion fluid entering the heart, mimic the effects of stimulation of the appropriate nerve (Raab and Humphreys, 1947; Barry, 1950) In the perfused heart the frequency of cardiac impulse-initiation by the S-A node is also increased by warming, by increased pH and by increased calcium ion concentration and is decreased by cooling, by decreased pH, and by increased potassium ion concentration.

When the S-A node is depressed, the A-V node often serves as the pacemaker. The frequency with which it generates impulses is effected in a manner similar to that of the sinoatrial node but to a lesser extent by the above-mentioned nerves. When the atrioventricular node was serv-

ing as the pacemaker, due to depression of the sinoatrial node, stimulation of the vagi frequently caused shift of pacemaker back to the sinoatrial node (Lewis, 1913-14; Meek and Eyster, 1913-14) Paes (1949) believes he has extracted a substance from nodal tissue which in the presence of epinephrine and acetylcholine initiates rhythmic activity in myocardial tissue.

The chronotropic sympathetic fibers supplying the sinoatrial node are readily blocked by tetraethyl ammonium ion (Parke, Davis and Co, Detroit). Those supplying the atrioventricular node, however, appear to be less readily blocked (Pardo *et al*, 1950).

Regulation of Rate of Conduction and of Duration of Refractory Period (Dromotropic Regulation)

Increased activity of the sympathetic nerves increases the velocity of conduction from atrium to ventricle, that is, shortens the atrioventricular interval (A_s-V_s interval in pulse curves and the PQ interval in the electrocardiogram). Sympathetic nerve stimulation may also increase the rhythmicity of the A-V node to the point where it, instead of the S-A node, becomes the pacemaker. When the A-V node serves as the pacemaker, impulses go forward from it through the special conduction system to excite the ventricle and backward to the atrium and eventually to the S-A node. The refractory period of the conduction tissue is shortened by sympathetic impulses. The refractory period is shortened in proportion to the increase in heart rate. The left sympathetic fibers appear to have greater effect on the A-V node than do the right.

Parasympathetic excitation slows the rate of conduction through the A-V node (incomplete heart block) and increases the length of the refractory period (partial heart block) (Lewis, 1913-14). The latter effect results in the occurrence of a 2.1, 3.1 or higher degree of block, *i e.*, only every other or every third atrial beat is transmitted to the ventricle (page 182). Very strong excitation of the vagal fibers, particularly of the right vagus, may cause complete cessation of atrial contractions, but after a short period of time ventricular contractions may occur at a slow rate. The ventricle is then said "to escape" from the vagal inhibition, the impulses arising from idioventricular centers This condition is designated as complete heart block with idioventricular rhythm (see page 177) Vagal impulses have no effect on the conduction of the impulse through the distal special conducting system or through the myocardium (Drury and Mackenzie, 1934a) but may depress conduction in the common bundle or its proximal branches (Drury and Mackenzie, 1934b)

Regulation of Excitability (Bathmotropic Regulation)

Duration of Refractory Period of Atrial and Ventricular Myocardium. Sympathetic impulses shorten the duration of *the contraction and the refractory periods* of atrial and ventricular systole (Wiggers and Katz, 1920). As would be expected from anatomic evidence, parasympathetic impulses have no demonstrable effect on the ventricle (Drury and Mackenzie, 1934a) It would seem that the vagal impulses would cause decreased excitability, lengthened refractory period and a slower rate of impulse conduction in the atrial myocardium. Lewis (1925) and Katz (1946) state, however, that if the ventricular rate is kept constant, vagal stimulation abbreviates the refractory period of the atria. Iglauer and associates (1941) and Nahum and Hoff (1935) noted that atrial fibrillation occurred more readily during parasympathetic activity, especially in association with thyroxin, and suggested

that this might be due to shortening of the refractory period

Effects on Threshold. During vagal stimulation or the injection of acetylcholine the excitability of atrial tissue is decreased, i.e., more energy is required to excite the tissue. This effect parallels that of the vagus and of acetylcholine on atrial contractility ([illegible] Garrey, 1931).

Regulation of Atrial and Ventricular Contractility. Inotropic Regulation

It has been thought that cardiac output was regulated solely by the pressure in the central venous reservoir, the output then being determined through the operation of the Starling mechanism (see pages 144 and 234). More recent studies suggest that the output of the heart may also be regulated by nervous and humoral mechanisms affecting the contractility of the atrial and ventricular myocardium.

Excitation of the vagus causes a decrease in the contractility of the atrial tissue; if the excitation is strong enough, atrial contraction may be abolished entirely (McWilliam, 1888, Wiggers, 1916-17). Provided that the ventricular contractions are artificially maintained at a constant rate, no effect is noted on ventricular contractility during vagal stimulation (Hiatt and Garrey, 1942-43). However, in the intact heart, vagal stimulation causes cardiac slowing with resulting greater diastolic filling and, therefore, greater stroke volume owing to the effect of the greater initial ventricular length (volume) on the stroke volume. Acetylcholine is said to have a direct stimulating effect on the ventricle (McDowell, 1945-46) which may be due to release of an epinephrine-like substance (Hoffmann *et al.*, 1945; Haney and Lindgren, 1945).

Sympathetic stimulation apparently increases the vigor of myocardial contraction for a given central venous pressure, *i.e.*, a given initial length, and results in a more abrupt contraction, a more nearly complete ejection and in shortening of systole. Similar effects follow injection of epinephrine (Ring *et al.*, 1949, Raab and Humphreys, 1947; Krop, 1944; Garb, 1950). Sympathetic stimulation and epinephrine appear to increase cardiac oxygen consumption more than they increase the work of the heart, in other words, they appear to decrease the efficiency of myocardial contraction (Raab and Lepeschkin, 1950).

An epinephrine-like substance can be extracted from normal cardiac muscle (von Euler, 1946). This substance is present in increased amounts after prolonged sympathetic stimulation and decreased after sympathectomy (Raab, 1947; Raab and Lepeschkin, 1950). The sympatholytic drugs Dibenamine, Priscoline and 933F* appear to protect the heart against excessive concentrations of these epinephrine-like substances (Raab and Humphreys, 1946). A similar protective effect is exerted by nitroglycerine (Raab and Lepeschkin, 1950).

The liver seems to be essential for maintenance of normal cardiac contractility but it is not known whether it supplies an essential hormone or metabolite or removes some depressant metabolic product (Poli and Rossi, 1950).

Central Mechanisms for Controlling Sympathetic and Parasympathetic Nerve Activity

Sympathetic Cardio-accelerator and Vasoconstrictor Centers. A paired bilateral set of neurons which are connected with the sympathetic fibers going to the heart

* Dibenamine is [illegible] th, Kline and French Laboratories, [illegible] through Ciba Pharmace[illegible] N. J.; and 933F was [illegible] then Professor [illegible] versity of [illegible]

are located in the reticular substance of the medulla. Electrical excitation of these neurons increases the intensity of the impulses going to the heart by way of the sympathetic nerve fibers and causes increase of heart rate. This medullary center is designated the *cardio-accelerator center*. Activity of a closely related center, the *sympathetic vasoconstrictor center*, causes arteriolar vasoconstriction which, in turn, causes elevation of arterial pressure when it is excited. Stimulation of the latter center probably also causes constriction of the vascular blood reservoirs and elevation of venous pressure. These two sympathetic centers, the accelerator and constrictor centers, act more or less concomitantly (Ranson, 1916; Ranson and Billingsley, 1916).

Parasympathetic Cardioinhibitory Centers. Located in the vagal nuclei in the medulla, close to the above-mentioned sympathetic centers is a paired parasympathetic center. Excitation of this center increases the intensity of the impulses in the vagal fibers and leads to cardiac slowing

Cardiovascular Regulatory Center. The above groups of centers, that is the accelerator, the constrictor, and the vagal centers, may be grouped together and designated the cardiovascular regulatory center. In general the sympathetic and parasympathetic centers operate reciprocally; anything that increases the activity of one tends to inhibit the activity of the other (Wickwire, 1920, Hunt, 1899; Wang and Borison, 1947). These centers are tonically active at all times, that is, are continually sending out impulses over their respective pathways. As a result, the heart may be speeded by increasing the sympathetic activity or by decreasing the parasympathetic activity. At normal resting heart rates, the vagal fibers are very active. Increase of heart rate to around 120 beats per minute is accomplished mainly by decreasing the vagal activity. Rates of 120 per minute can, for instance, be induced by blocking the vagal impulses by large doses of atropine. Increase of heart rate to 150 per minute and especially above this rate requires, in addition, augmented sympathetic nerve activity (Tulgan, 1926, Hunt, 1899)

Factors Affecting the Medullary Centers. Direct Effects of Change in Composition of Blood. Increase of carbon dioxide tension, decrease of oxygen tension, or decreased pH from the normal level of the blood flowing by the medullary cardiovascular regulatory center tends to cause speeding of the heart by inhibiting the vagal and exciting the cardioaccelerator and vasoconstrictor centers. The net effect is to cause a rise in both arterial and central venous pressures and an increase in cardiac output To some extent reverse changes in the circulatory system are produced by decreased CO_2 tension or increased O_2 tension or pH.

Reflex Effects from the Chemoreceptors. The carotid bodies located near the point of origin of the internal carotid arteries and the aortic bodies located near the arch of the aorta are irrigated by the systemic arterial blood. Sensory endings are located in these structures which are excited by increase of CO_2 tension or by decrease of O_2 tension or pH. Impulses discharged from these sensory endings are conveyed, respectively, by the ninth and tenth cranial nerves to the above-mentioned medullary centers where they augment the effects of the changes in blood composition.

Reflex Effects from the Pressoreceptors. Sensory endings are located in the walls of each common carotid artery near the origin of the internal carotid artery and in the arch of the aorta. These endings are excited in proportion to the level of the arterial blood pressure. Elevation of arterial pressure leads to increased intensity

of the afferent nerve discharges which are conveyed from the sensory endings to the medulla by way of the ninth and tenth cranial nerves, respectively (Nonidez, 1935). These impulses in turn cause inhibition of the cardio-accelerator and vasoconstrictor centers and excitation of the cardioinhibitory (vagal) center. The afferent fibers are designated the moderator or depressor fibers since electrical excitation of them causes a fall of arterial pressure and slowing of the heart and since cutting the fibers causes a permanent neurogenic hypertension and cardioacceleration

Pressure receptors are also thought to be present in the venae cavae and pulmonary veins which are stimulated by an increase of pressure in these vessels. Increase in their afferent impulses causes cardiac acceleration (Sassa and Miyazaki, 1920, Nonidez, 1937). This effect is called the Bainbridge reflex (Bainbridge, 1915).

Other Regions in the Nervous System which Affect the Medullary Centers. Impulses over nerves from the hypothalamic centers integrate the activity of the medullary cardiovascular regulatory center in the regulation of body temperature and in emotional reactions, *i.e.*, the tachycardia associated with anxiety. Impulses from the motor areas of the cerebral cortex (Hoff and Green, 1936; Green and Hoff, 1937; Fulton, 1949) and probably also impulses from contracting muscles alter the activity of the medullary centers so as to improve the blood flow in the skeletal muscles during physical exertion. The medullary centers are also affected by impulses from the respiratory centers, the heart rate tending to vary with respiration; by afferent impulses in the minor splanchnic nerves which, when stimulated, cause a fall in arterial pressure (Burton-Opitz, 1916-17), and by afferent fibers in many sensory nerves, probably pain fibers, which, when electrically stimulated, cause a rise of arterial pressure.

Influence of Potassium and Calcium. Increase of potassium ion tends to slow the heart and to cause decreased contractility. Increase of calcium ion causes speeding and increased contractility, excessive concentrations of calcium prevent full relaxation of the ventricles during diastole (Hiatt and Garrey, 1942-43, Harris and Madjerek, 1948, Friedman and Biné, 1947).

6. MYOCARDIAL METABOLISM AND CORONARY CIRCULATION

It is extremely difficult to secure exact figures for the coronary blood flow and particularly for the myocardial metabolism with the heart normally functioning *in situ*. Most data have been obtained from isolated perfused hearts, or at best by simultaneous measurement of the composition of and rate of coronary artery inflow and the composition of the coronary sinus venous outflow of blood in the animal with chest cavity exposed. Recently, however, a technic has been developed for estimating coronary flow from the rate of uptake of nitrous oxide by the myocardium, by measurement of successive differences in concentration of this substance in the systemic arterial and coronary sinus venous blood, while inhaling low concentrations of the gas. This method gives results which, fortunately, are comparable with the direct methods and makes possible for the first time extension of the studies to man (Eckenhoff and Hafkenschiel, 1947, Eckenhoff *et al*, 1947, 1948; Bing *et al.*, 1947, 1949; Brown and Pearson, 1947; Culbertson *et al*, 1949). From simultaneous recordings of coronary artery inflow using the rotameter and the nitrous oxide method, Gregg and associates (1951) conclude that the latter has an average accuracy of $\pm$ 12.4 per cent (extremes $+$ 21 to $-$ 22 per cent).

Myocardial Metabolism. Under conditions of high blood sugar levels the myocardial respiratory quotient approaches 1.0, suggesting that carbohydrate serves as the primary source of fuel. Goodale and associates (1950) found in man a normal nonfasting respiratory quotient of 0 89 to 0 93. Oxidation of glucose, lactate and pyruvate, computed from arteriovenous differences in concentration, accounted for 90 to 100 per cent of the simultaneously measured oxygen uptake As blood sugar falls the respiratory quotient shifts towards 0.7 (Cruickshank and Startup, 1934a, Evans *et al*, 1934a, b, Goodale *et al.*, 1950). Under the latter conditions, myocardial fat, blood fatty acids or ketones may be consumed (Cruickshank and McClure, 1936, Waters *et al.*, 1938; Visscher, 1938, Barnes *et al*, 1938; Cruickshank and Kosterlitz, 1941, Haynes and Weiss, 1940, Pearson *et al*, 1949a, b; Nakamura *et al.*, 1949) Amino acids do not appear to serve as a substitute fuel (Cruickshank, 1936)

In the presence of severe diabetes the myocardial respiratory quotient may also approach 0.7, with glucose oxidation virtually absent. Addition of insulin raises the respiratory quotient to 1 0 without changing the oxygen uptake (Cruickshank and Startup, 1934b).

Myocardial glycogen is reduced slightly (20 per cent reduction) by lowering of blood glucose levels. When epinephrine is added, myocardial glycogen rapidly disappears. After such reduction, glycogen levels can be restored by addition of glucose but not of lactic acid to the perfusate (Bogue *et al*, 1937, 1938, Fletcher and Waters, 1938). Myocardial glycogen content varies with blood ketone levels, but not with blood glycogen or lactic acid levels, in animals that have first been fasted, then given butyric acid or glucose in the diet (Lackey *et al*, 1946). Myocardial glycogen invariably increases from a normal level of 0 6 to the order of 1.25 Gm. per 100 Gm. of muscle in diabetes and is reduced by addition of insulin, whereas administration of insulin to normal animals increases myocardial glycogen (Cruickshank, 1936).

The normal heart consumes considerable quantities of both lactate and acetate (Lorber *et al*, 1945-46, McGinty and Miller, 1933, Cruickshank and Kosterlitz, 1941) During gradual reduction of its oxygen supply the heart continues to use glucose and lactate Failure suddenly occurs with oxygen tensions of 15 to 30 mm. of mercury at which time the heart begins converting glucose to lactic acid, with outward instead of inward diffusion of the latter (McGinty, 1931, Evans *et al*, 1934c) Under these conditions survival is prolonged by elevation of blood glucose concentration but not by increase of lactic acid levels (Bogue *et al*, 1938)

Phosphorus metabolism appears to parallel that of skeletal muscle, adenosine triphosphoric acid and phosphocreatine (phosphogen) serving as phosphorus donors, and adenylic acid and creatine as phosphorus acceptors (Wollenberger, 1949) In asphyxia and aglycemia a marked decrease in phosphogen occurs in ventricular muscle (Cruickshank, 1936).

Digitalis and related compounds, cholesterol, estrone, testosterone, and alpha tocopherol (vitamin E) protect the myocardium against anaerobic breakdown of coenzyme I (Govier *et al*, 1946). The effects of cardiac glucosides upon the energy metabolism of the heart are reviewed in great detail by Wollenberger (1949).

Normal Values for Myocardial Oxygen Consumption. The difference between systemic arterial and coronary sinus venous blood oxygen content is larger than for any other organ under resting conditions, and is of the order of 11 to 19 ml of oxygen per 100 ml. of blood flow (Bing *et al.*, 1947, Culbertson *et al.*, 1949). This figure,

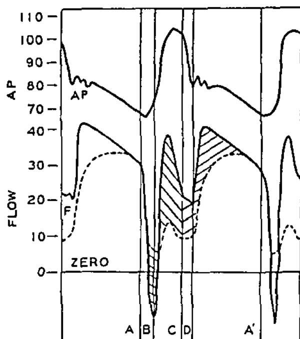


Figure IV-5 Simultaneously recorded curves of aortic pressure *AP*, of the instantaneous rate of flow into the left descending coronary artery, solid line *F*, and of the assumed flow *through* the myocardial capillaries, interrupted line Scales at left *AP*, aortic pressure in mm Hg, *FLOW*, blood flow in ml /min *A*, *A'*, onset of isometric contraction, *B*, onset of ventricular ejection, *C*, onset of protodiastole, *D*, incisura, onset of isometric relaxation (Redrawn after Gregg and Green, 1940)

combined with that for the rate of coronary blood flow of 70 ml. per minute gives an oxygen uptake by the myocardium of the order of 7 to 10 ml. per minute per 100 Gm. of myocardial weight for man (Bing *et al.*, 1949) and 9 to 24 ml./100 Gm./min. for dogs (Spencer *et al*, 1950), which is exceeded only by the kidneys (18 ml. per minute per 100 Gm) and possibly by the thyroid gland (Green, 1950). Under resting conditions the heart appears to account for about 9 per cent of the total oxygen consumed by the body (Green, 1950).

Normal Values for Coronary Blood Flow. In dogs the heart weighs approximately 7.5 Gm. per kilogram of body weight, in man the heart appears to be relatively slightly smaller, the figure frequently quoted being 300 grams for an average man of 60-kilogram weight or 5 grams per kilogram. The most satisfactory estimates at present place the normal flow at 55 to 70 ml. per minute per 100 Gm. of heart weight or approximately 120 ml. per minute per square meter of surface area, that is, under resting conditions the total coronary blood flow is of the order of 4 to 5 per cent of the cardiac output per minute (Eckenhoff *et al.*, 1947, 1948; Bing *et al.*, 1949, Green, 1950b).

Instantaneous Coronary Blood Flow. The flow of blood into the coronary artery at each instant in the heart cycle may be recorded with a suitable flowmeter (Gregg and Green, 1940). An example of a record obtained with such a meter is reproduced in Figure IV-5. The solid line represents the recorded flow into the anterior descending coronary artery, the broken line the probable intramyocardial flow. The coronary artery inflow during late diastole is rapid. With the onset of isometric contraction (IC) the inflow rapidly decreases and backflow from the coronary capillaries is often noted. The backflow abruptly ceases and forward flow is established when the onset of ventricular ejection (VE) causes the aortic pressure to rise. The initial rapid flow begins to decrease at the height of the aortic pressure and reaches a plateau in the latter part of systole at which level it remains throughout the remainder of systole and protodiastole With the onset of isometric relaxation (IR) the coronary artery inflow again rapidly increases, reaches a peak approximately at mid-diastole and then declines progressively until the onset of the next isometric contraction.

When systole begins, the myocardium compresses the contents of the ventricular cavities, raising the pressure therein. As a consequence, tension is built up in the ventricular walls. This tension equals the intraventricular tension in the innermost layers of the myocardium and gradually decreases towards zero in the outermost

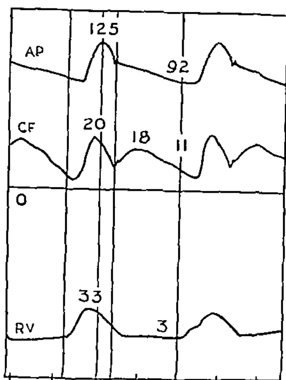


Figure IV-6 An example of flow into the right coronary artery measured with the orifice meter for "instantaneous rate of flow" In top curve, *AP* indicates aortic pressure and figures represent maximum and minimum pressures in mm Hg In middle curve, *CF* indicates coronary flow and figures represent rate of flow in ml/min at the indicated points The *O* line indicates the position which the top of the flow curve would occupy at zero flow In the bottom curve, *RV* indicates right intraventricular pressure and figures represent the maximum and minimum pressures in mm Hg (Reproduced from Gregg, 1950, by courtesy of Lea and Febiger, Philadelphia)

layers of the ventricular walls The tension developed in the ventricular wall produces strong extravascular compression of the coronary blood vessels, with a consequent increase in the resistance to flow through these vessels. As the myocardium contracts, it also squeezes blood out of the capillaries into the coronary arteries. These two factors cause a rapid reduction in inflow (Jochim, 1940). The sharp rise in flow at the beginning of ventricular ejection is caused primarily by the uptake of blood in the superficial coronary vessels with the rise in aortic pressure The actual flow through the myocardial capillaries probably increases only slightly during this period, as is indicated by the broken line in Figure IV-5. The shaded area between the two curves represents the volume of blood taken up in the superficial arteries. The backflow occurring during isometric contraction is caused by the squeezing of blood out of the capillary vessels back into the arteries. At the same time, of course, blood is flowing forward into the coronary sinus. This flow has been recorded by means of venous outflow meters. The initial rapid inflow of blood into the coronary artery with the onset of isometric relaxation is in part due to the uptake of blood to fill the previously compressed capillaries. This is indicated by the shaded area between the solid and broken lines During the more stable periods of flow in the latter parts of diastole and of systole, the inflow probably coincides relatively closely with the actual intramyocardial or capillary flow. During the other phases of the cycle the inflow differs from the capillary flow The instantaneous blood flow through the myocardium can, therefore, be computed accurately only during the latter part of systole and at the end of diastole The effect of drugs on the portions of the coronary vessels which regulate coronary blood flow can be estimated accurately, therefore, only by measuring the blood flow at these instants in the heart cycle (Gregg and Green, 1940, Katz *et al.*, 1938a).

The instantaneous flow in the circumflex branch of the left coronary artery is essentially similar to that described above for the anterior descending branch. That in the right coronary artery, reproduced in Figure IV-6, undergoes changes qualitatively similar to those in the left coronary artery throughout the heart cycle, but the reduction in flow in systole is proportionally much less because of the lower intramyocardial tension in the right ventricular wall. The lower intramyocardial systc'

tension is associated with the lesser systolic intraventricular tension in the right as compared with the left ventricle (Gregg *et al.*, 1943; Gregg, 1950). Records of flow in the right atrial myocardium show reduced flow during atrial systole (Smith and Layton, 1946).

Relation of Coronary Blood Flow to Myocardial Metabolism. Ordinarily the venous blood returning from most regions of the body has an oxygen content of around 14 volumes per 100 ml. blood, *i e*, the oxygen utilization amounts to approximately 30 per cent As noted above, however, the venous blood draining from the coronary sinus has an oxygen content of about 6 to 8 volumes per 100 ml blood, indicating an oxygen utilization of the order of 65 per cent It is, therefore, obvious that increased metabolic demands by the myocardium must be met principally by an increased coronary blood flow rather than an increase in the oxygen utilization.

Studies indicate that the coronary blood flow under varying conditions increases approximately in proportion to the cardiac work and the intraventricular pressure, as would be postulated from the above data (Brown and Pearson, 1947). This increased coronary blood flow is produced in part by the elevation of arterial pressure which frequently accompanies increased cardiac work. However, the increase in flow is usually more than that of the arterial pressure and must, therefore, be due to dilatation of the arterioles and small terminal arteries which regulate the coronary blood flow (Gregg and Shipley, 1944; Gregg, 1946). It is known that the coronary blood flow can be markedly increased either by reduction of the oxygen content of the inspired air or by intracoronary injection of sodium cyanide; after ischemia of as short a duration as five seconds, the blood flow increases significantly, and after ischemia of 30 to 60 seconds the blood flow is doubled. It is, therefore, apparent that local metabolic regulation of the blood flow is an extremely important factor (see Figure IV-7). This regulation is probably primarily dependent upon the oxygen supply, inasmuch as an increase in the concentration of carbon dioxide in the inspired air will produce some cardiac slowing but has no effect on the blood flow at the end of diastole and, therefore, practically no effect on the myocardial arterioles (Green and Wegria, 1942). It has been postulated that increased coronary flow accompanying cardiac acceleration is caused by a greater massaging action of the myocardium. However, since increased cardiac rate means proportionally greater time per minute in systole than in diastole and since in systole the coronary flow is less than in diastole, it would be anticipated that cardiac acceleration *per se* should reduce the coronary blood flow per minute. Since it does not, it must be postulated that the increased flow is due to a dilatation of the arterioles which in turn is probably a response to the increased metabolic activity of the myocardium (Cohn and Steele, 1935, Katz *et al*, 1945a) Foltz and coworkers (1950) studied the relation of coronary flow to a large number of variables and found that coronary flow most closely paralleled cardiac oxygen consumption. They concluded the most important factor regulating coronary flow was the myocardial metabolism.

Nervous and Chemical Control of Coronary Blood Flow. Shipley and Gregg (1945) have recorded the coronary inflow while stimulating the stellate ganglia Under these conditions, the coronary blood flow increases, particularly in diastole, indicating an apparent vasodilation. Our own studies with intracoronary injections of varying concentrations of epinephrine indicate a similar phenomenon (Figure IV-10C). No reduction in coronary inflow was ever noted at the end of diastole with administration of doses of epine-

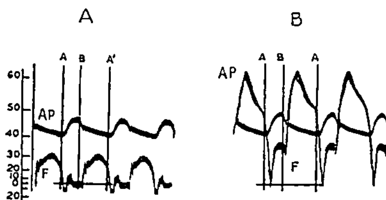


Figure IV-7 Segments of records showing effects of asphyxia upon the coronary blood flow *AP*, aortic pressure, *F*, blood flow in descending ramus of left coronary artery, scale at left gives rate of flow in ml /min , figures below zero are for backflow The studies were performed upon a dog with chest opened, under morphine and sodium barbital anaesthesia Asphyxia was produced by stopping the artificial respiration During the control periods (left-hand record *A*) aortic pressure was 93/52, the heart rate was 135/min. and the *average* coronary flow was 17 5 ml /min At the height of the asphyxial effect (right-hand record *B*), 1 min 40 sec after onset of asphyxia, the aortic pressure was 104/56, the heart rate was 121/min , and the *average* coronary flow was 45 8 ml /min (Reproduced with modifications, from Green and Wegria, 1942)

phrine from 0 01 to 100 μg. On the other hand, with increasing doses a progressive *increase* in coronary flow at the end of diastole was recorded These findings suggest that epinephrine has a pure vasodilator effect on the coronary arterioles It was observed, however, that when the coronary artery was perfused under a constant head of pressure, the initial effect of the intra-arterial epinephrine injection was a reduction in the coronary inflow during isometric contraction which must be interpreted as an indication that the epinephrine had stimulated the myocardium to a more vigorous contraction. The increased blood flow in diastole gradually followed the initial myocardial stimulation It is possible, therefore, that the vasodilator effect of epinephrine may be, in part at least, secondary to the enhanced myocardial metabolism which accompanies the stimulation of the myocardium to increased vigor of contraction (Green *et al*, 1942b; Shipley and Gregg, 1945). Eckstein and co-workers (1950) felt that mechanical massage played no part in the increased flow that followed sympathetic nerve stimulation, and that at most 30 per cent of the increase could be due to change in the duration of systole relative to the cycle length. They did not indicate what they thought was responsible for the active vasodilation which was responsible for the remaining 70 per cent of the increased flow.

Stimulation of the vagus and injection of the acetylcholine group of drugs have given variable results When total coronary flow is measured it is found to be reduced, and conversely, coronary flow increases after vagal section (Anrep and Segall, 1926). Registration of the coronary artery inflow, however, with a pulsatile type of flowmeter, indicated to us no significant change in the flow at the end of diastole despite considerable cardiac slowing. We were, therefore, unable to demonstrate the presence of either constrictor or dilator fibers in the vagus of the dog (Green *et al.*, 1942a).

Gollwitzer-Meir and Kroetz (1938) have studied the effect of nerve stimuli on the

relationship between blood flow and myocardial metabolism. Their data, based on measurements of the difference in oxygen content between coronary arterial and venous blood and the coronary blood flow, suggest that under the influence of sympathetic stimulation the blood flow increases less than does the oxygen uptake; as a result, the arterial-venous difference in oxygen content is increased, and the increase in total oxygen uptake is relatively greater than the increase in cardiac work, indicating that sympathetic stimulation decreases myocardial efficiency. On the contrary, parasympathetic stimulation decreased the oxygen uptake in proportion to the work of the heart and, therefore, may be said to have increased myocardial efficiency (see also Raab and Lepeschkin, 1950)

Reports have appeared at various times suggesting that coronary flow can be influenced reflexly by impulses arising in various parts of the body (Gilbert *et al*, 1940), especially the abdominal viscera and gallbladder, but considerable doubt still remains regarding the importance of such reflexes.

Effect of Drugs on Coronary Circulation. The only drug which unequivocally causes coronary arteriolar constriction and reduces coronary blood flow is Pitressin. When injected directly into the coronary artery the coronary flow may be reduced so much that the contractility of the myocardium, supplied by the artery which is injected, may be seriously impaired (Green, 1940; Green *et al*, 1942b). (See Figures IV-8, 10). High concentrations of potassium and presence of blood of foreign species also cause coronary vasoconstriction (Katz *et al*, 1938a, b, c, Katz, 1939). We also have noted that blood from cattle causes prompt reduction in the flow through the dog's coronary vessels (unpublished observations).

The coronary flow is significantly increased and the coronary arteriolar constriction greatly reduced after either intravenous or intracoronary arterial injections of the xanthines (Figures IV-9, 10) and the nitrite group of drugs (Figure IV-10) (Green, 1940; Lindner and Katz, 1941; Boyer and Green, 1941; Raab and Humphreys, 1947) and papaverine (Lindner and Katz, 1941). The beneficial effect of the nitrites may be due, however, not only to their coronary vasodilator influence but also to diminution in the cardiac output and cardiac work by causing peripheral pooling of the blood, and by counteracting certain toxic effects of epinephrine on the heart (Raab and Humphreys, 1946, 1947). The adrenolytic drugs Dibenamine, Priscoline, and 933F (see page 152) also protect against excessive concentrations of epinephrine (Raab and Humphreys, 1946).

Myocardial Capillaries. The myocardial capillaries run parallel to the muscle fibers, *and are of such number that normally each* muscle fiber lies in direct contact with one or more capillaries. Hypertrophy, developing because of cardiac disease, causes enlargement of the muscle fibers without increase in the capillaries and, as a consequence, the capillary supply per unit volume of heart muscle is decreased (Wearn, 1928, Shipley *et al*, 1937, Wearn, 1941, Gregg, 1946).

Collateral Communications. Small arterial communications exist between the smaller branches of the coronary arteries, between the main coronary arteries, and to some extent between the coronary arteries and the extracardiac structures. These communications are quite small, of the order of 40 micra (Schlesinger, 1938). In the dog the communications between the main coronary arteries are principally superficial (Bobb *et al*, 1948). Immediately after occlusion of a main coronary ramus they would probably be sufficient to transmit only 2 to 5 per cent of the normal inflow of the occluded artery

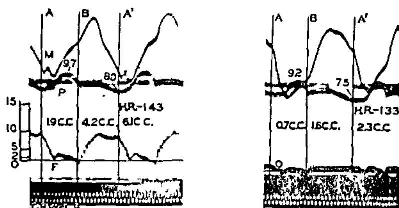


Figure IV-8 Effect of intra-arterial injection of 1 unit of Pitressin upon the blood flow in the descending branch of the left coronary artery and upon the contractility of the myocardium supplied by this branch *M*, myocardiographic record, upward movement indicates shortening, downward movement indicates lengthening of the myocardial fibers, *P*, aortic pressure, the figures adjacent to the curve give the systolic and diastolic pressures in mm Hg, *F*, blood flow in the descending branch of the left coronary artery, scale at left gives the instantaneous rate of flow in ml /min, figures give the average flow per minute during systole (*A-B*), and during diastole (*B-A'*) *A*, onset of isometric contraction, *B*, onset of protodiastole During the control period the heart rate was 143 min, and the average flow was 6.1 ml / min, at the height of the drug effect the heart rate was 133/min, and the average flow was 2.3 ml /min Note that during the control period the muscle shortened during ventricular ejection and lengthened during diastole, whereas at the peak of the drug effect (*B*) the muscle fibers lengthened during isometric contraction and shortened during isometric relaxation, *i e*, they acted like elastic instead of muscle fibers (Reproduced in modified form from Green, Wegria and Boyer, 1942)

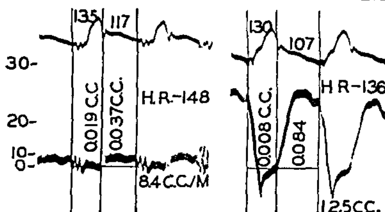
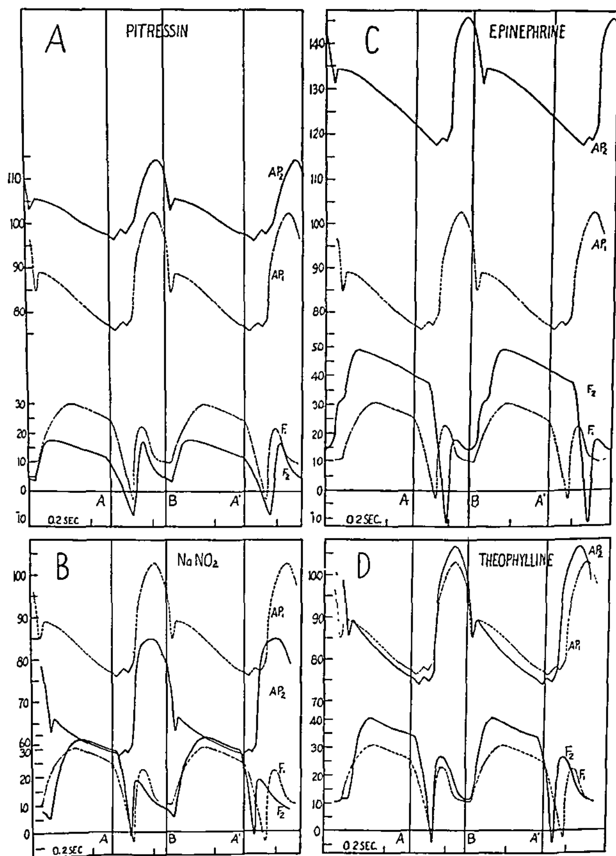


Figure IV-9 Response to intracoronary arterial injection of 5 mg of theophylline monoethanolamine Left-hand record, control, right-hand record,

tole respectively The average control flow was 8.4 ml /min, and the maximum average flow produced by the drug was 12.5 ml /min Scale at left, instantaneous rate of flow in ml /min, read to the top of the flow line. *H R*, heart rate Note the reduction in flow during systole, despite the increase in flow during diastole (Reproduced in modified form, from Boyer and Green, 1941)


A
PITRESSIN
AP2
AP1
F1
F2
A
B
A'
0.2 SEC
C
EPINEPHRINE
AP2
AP1
F2
F1
A
B
A'
0.2 SEC.
B
Na NO2
AP1
AP2
F1
F2
A
B
A'
0.2 SEC
D
THEOPHYLLINE
AP2
AP1
F2
F1
A
B
A'
0.2 SEC.

(Wiggers and Green, 1936). After progressive gradual occlusion, however, these communicating channels enlarge, until they are capable of supplying 50 to 100 per cent of the normal inflow (Gregg *et al*, 1939). Communications are seen between the myocardial vessels and the ventricular cavities (arterio-luminal vessels). While they may serve as accessory paths for venous drainage, it is unlikely that they can serve as sources of arterial blood for the nourishment of the myocardium (Gregg, 1946).

Electrical Activity of the Heart. For a discussion of the electrical activity of the heart, see standard reference books on electrocardiography (Graybiel and White, 1946, Katz, 1946, 1947, Goldberger, 1947, Burch and Winsor, 1949, Hecht, 1950, Wolff, 1950).

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←Figure IV-10 Graphs of the typical effects of intravenous injections of various drugs on the aortic pressure, *AP*, and on the blood flow in the descending branch of the left coronary artery, *F*, in dogs Subscript 1 and dotted lines indicate control pressures and flows, subscript 2 and solid lines the pressures and flows during the peak effect of the drug on the coronary flow. *A*, 1 unit Pitressin, *B*, 30 to 100 mg $NaNO_2$, *C*, 10 to 100 μgm epinephrine, *D*, 20 to 50 mg theophylline Scales at left upper, aortic pressure in mm Hg, lower, coronary artery blood flow in ml/min The ordinates are drawn as for the control curves, *A*, *A'*, onset of isometric contraction, *B*, onset of protodiastole Note Pitressin reduced the flow throughout the heart cycle despite an increase in aortic pressure, the nitrites increased the flow despite a marked drop in aortic pressure, epinephrine increased coronary flow during diastole approximately in proportion to the elevation of aortic pressure, backflow during isometric contraction being accentuated, theophylline increased the diastolic flow despite a slight reduction in aortic diastolic pressure.

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Physiology of the Heart

B. Abnormal Cardiac Function

1. CARDIAC IRREGULARITIES

THIS TOPIC will be discussed systematically according to the mode of origin of the irregularities The presentation will then be concluded by a table which regroups the irregularities according to their presenting clinical symptom.

Disturbances in Initiation of Impulse

RHYTHMS ARISING IN SINO-ATRIAL NODE

Sinus Tachycardia. In adults the heart has a normal sinus rhythm and a rate that lies between 60 and 100 beats per minute An increased frequency of impulse initiation is due primarily to decrease in vagal inhibition of the sinus node. Above a rate of 100 per minute, there is probably also an increased discharge of sympathetic accelerator impulses to the sinoatrial node Electrocardiographic tracings taken during sinus tachycardia are normal except for shortening of the P-Q interval and curtailment of diastole of the heart cycle. No abnormalities are noted in the heart sounds or pulse tracings. The tachycardia may be initiated by exercise, anoxia, emotion, or the administration of atropine, amyl nitrite, snake venom (Glass, 1949) or thyroxin, and may appear in thyrotoxicosis, heart failure, shock, hemorrhage and hyperthermia, and possibly during excessive use of alcohol and tobacco. In all cases, it is due to the excessive frequency with which the sinoatrial node is initiating cardiac impulses Both onset and disappearance are usually gradual, and the tachycardia may persist from seconds to days. Sinus tachycardia is commonly seen in persons with neurocirculatory asthenia.

Sinus Bradycardia. Like sinus tachycardia, sinus bradycardia may be either transient or prolonged, and may appear and disappear gradually or fairly rapidly. Sinus bradycardia is considered to be present if the cardiac rate lies between 45 and 60 per minute. It occurs frequently during sleep and is commonly encountered in persons who have trained in physical exercise and have some physiologic cardiac hypertrophy. It may be induced reflexly by stimulation of the sensory endings in the respiratory tract during inhalation of irritant gases, by excitation of pain endings by pressure on the eyeballs, or by activation of pressor receptor

ings through pressure upon the carotid sinus. Bradycardia is observed in association with increased intracranial pressure, jaundice and epidemic parotitis, during recovery from influenza, and as a result of administration of an excess of digitalis or quinidine and during excessive cooling of the body. Except for prolonged P-Q and Q-Q intervals, the electrocardiographic and pulse tracings are normal.

Sinus Arrhythmia. Sinus arrhythmia represents speeding and slowing of the heart rate which is usually coincident with respiration, speeding during inspiration and slowing during expiration (phasic sinus arrhythmia). It is more marked in the young than in the aged, and is thought to be due to impingement upon the cardioregulatory center of afferent impulses from the lungs carried by way of the vagi, *i e*, by the Hering-Breuer fibers. Variations in the heart rate may also accompany Cheyne-Stokes respiration. The pulse and electrocardiogram are normal except for the variations in rate and corresponding variations in the P-Q intervals and in the duration of diastole Sinus arrhythmia is abolished by factors which decrease vagal tone, as by exercise, atropine and hemorrhage.

In nonphasic sinus arrhythmia the variations in heart rate do not coincide with the respiratory rhythm Such arrhythmia may be seen also in sinus standstill, shifting or wandering pacemaker or sinoatrial block (see pages 177, 182). Sinus standstill may last for various intervals of time It may be distinguished from sinoatrial block by determining that the pauses are not a multiple of the normal P-P interval. During sinus standstill the atrioventricular node may take over the function of the pacemaker. The pacemaker function apparently may shift also from one to another portion of the sinoatrial node. In such cases the P waves remain upright and the P-Q intervals are longer than 0.12 second (Katz, 1946).

PASSIVE RHYTHMS OF ECTOPIC ORIGIN

Rhythms of passive ectopic origin are those occurring at a rate of 80 or less per minute They are usually caused by failure of the sinoatrial node to maintain a normal rate of impulse initiation with the result that a lower center takes over the function of impulse initiation.

Atrioventricular Nodal Rhythm. An atrioventricular nodal rhythm is seen in conditions in which the sinoatrial node fails to act as pacemaker The rhythm is regular but the rate is usually slower than in sinus rhythm, *i e*, from 30 to 50 beats per minute The commonest cause of A-V nodal rhythm is depression of the S-A node by vagal activity; this rhythm may be seen also after administration of excess digitalis and in arteriosclerotic heart disease. The genesis of the heart beat may be returned to the sinoatrial node as a result of exercise or administration of atropine When the impulses arise in the uppermost portion of the atrioventricular node a *coronary* rhythm is said to be present.* The P-Q interval is usually less than 0.10 second and the P wave may be upright in leads I and II *Upper nodal* rhythm is said to be present with P-Q intervals of the order of 0.01 to 0.02 second, *middle nodal* rhythm when the P wave is buried in the QRS complex, and *lower nodal* rhythm when the P wave follows the QRS complex giving a Q-P interval which is not measurable or measures from 0 02 to 0.1 second. In the latter three rhythms, the P wave is usually inverted in leads II and III, because of the reversed direction of spread of the impulse over the atrium, which causes the initial region of negativity to be closer to the left leg and the left arm than to the right arm as is normally the case. The atrial wave (A wave) in the jugular venous pulsation will tend to be superimposed on the ventricular

* Ruskin and Decherd (1945) believe that this rhythm is actually a sinus rhythm with a relatively rapid conduction through the A-V junctional tissue.

ejection wave (C wave). Aberrations have been noted in the P-Q intervals and in the QRS-T complexes following premature atrial beats (Berliner and Lewithin, 1945) In the presence of nodal rhythm, the electrocardiogram may be modified by the simultaneous occurrence of delayed conduction in the atrioventricular node, the retrograde impulse also may be blocked before it reaches the atrium.

Wandering Pacemaker. Under certain conditions the pacemaker function may wander back and forth between the sinoatrial node and the atrioventricular node, probably because of rhythmic depression and enhancement of activity in the sinoatrial node. Indicative of such shifts will be the characteristic slowing of the heart rate and inversion of the P waves and shortening of the P-Q intervals in the electrocardiogram, usually to less than 0 10 second, whenever the atrioventricular node becomes the pacemaker. Such shifting may be the result of varying intensity of the vagal nerve impulses impinging on the sinoatrial node (Levine *et al*, 1949)

Idioventricular Rhythm. An idioventricular rhythm is usually seen only during complete heart block (see page 183) Under these conditions the ventricular rate is commonly around 30 beats per minute. The impulse originates below the atrioventricular node (as evidenced by the lack of retrograde conduction to the atrium) but above the branching of the Purkinje system, since normal QRS-T complexes are recorded. Idioventricular rhythms are not affected by exercise, usually begin suddenly, and are associated with myocardial damage, severe infections, influenza, typhoid fever, diphtheria, pneumonia and coronary arterial disease. The atria usually continue beating at a normal rate which is completely independent of the ventricular rhythm. An idioventricular rhythm may occasionally develop with very strong vagal stimulation; presumably it may be induced by excessive doses of drugs which excite the tissues supplied by the parasympathetic nerves Idioventricular rhythm may originate below the branching of the Purkinje system, or the impulse may originate above the bifurcation in a person with pre-existing bundle branch block, in either case, the QRS complexes are abnormal and resemble those of premature ventricular beats.

ACTIVE ECTOPIC RHYTHMS

Active rhythms are those which occur when some part of the heart gives rise to an impulse at an interval, following a previous beat, which is shorter than the normal interval between two sinoatrial impulses If this occurs only occasionally and for brief intervals, premature beats result; with more prolonged enhancement of ectopic impulse initiation, paroxysmal tachycardias are produced. A premature beat may arise in the atrium, the atrioventricular node or the ventricle A premature beat may arise very soon after a previous contraction of the heart. It has been postulated that such initiation represents either (1) a hyperirritable focus in which the impulse initiation occurred early in the period of recovery (Prinzmetal *et al*, 1950) or (2) an area of depressed irritability which did not respond to the preceding impulse and subsequently generated its own beat, or conducted the impulse so slowly that it arrived at the opposite side only after the adjacent tissue had fully recovered from the preceding beat (Mack and Langendorf, 1950; Di-Palma and Schultz, 1950).

Premature Atrial Beats. A premature atrial beat usually spreads to and activates the sinoatrial node. As a result the rhythm of the beat is interrupted and in essence stepped forward by the shortening of the interval from the preceding normal beat to the premature beat. The interval from the beginning of the premature beat to the next

ings through pressure upon the carotid sinus. Bradycardia is observed in association with increased intracranial pressure, jaundice and epidemic parotitis, during recovery from influenza, and as a result of administration of an excess of digitalis or quinidine and during excessive cooling of the body. Except for prolonged P-Q and Q-Q intervals, the electrocardiographic and pulse tracings are normal

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rate usually ranges between 120 and 200 beats per minute though rates as high as 300 may be seen; the rhythm is regular Paroxysmal tachycardias usually start and end abruptly; occasionally they may be stopped with exercise, pressure on the carotid sinus, deep breathing or administration of Mecholyl or a pressor drug (Youmans *et al.*, 1947). It is reported (Tandowsky, 1945) that Lantoside C, administered intravenously, may stop the paroxysms and that it may prevent their recurrence when given in maintenance doses. Quinidine was found to stop 46 of 57 episodes (Armbrust and Levine, 1950). The rate however, does not vary with exercise. If the rate slows with pressure on the carotid sinus, it usually remains slow upon release of pressure The patient may notice nothing or may have an attack of angina, fainting, sudden collapse, shock, dyspnea or mild heart failure, as a result of the tachycardia. Such tachycardias may be associated with fatigue, exercise, excessive use of tobacco or alcohol, indigestion, infections or heart disease, especially rheumatic heart disease (Kissane *et al.*, 1950), or administration of digitalis A series of rapid premature atrial beats may result from a single electrical shock applied to the atrium in the "vulnerable period" during the relatively refractory period of the atrial cycle (Orias *et al*, 1950). With increased intensity of the shock, atrial fibrillation may result (see page 180). A two-to-one block or bundle branch block may be seen during very rapid atrial paroxysmal tachycardia.

Ventricular tachycardias show essentially the same rates as atrial and they are often associated with the presence of organic heart disease. In 74 per cent of instances the cause was coronary disease (Armbrust and Levine, 1950). Experimentally ventricular tachycardia may occur in the presence of hyperexcitability of idioventricular pacemakers due to epinephrine, with stretching of the myocardium due to a sudden increase in pressure, plus inhibition of higher pacemakers through vagal stimulation (Lenel *et al*, 1948). Digitalis is contraindicated in ventricular tachycardia since it may induce ventricular fibrillation (Katz, 1946) Quinidine appears to be partially successful in abolishing the tachycardia that follows ligation of a coronary artery in dogs, but only with large doses that frequently produce vomiting (Harris *et al*, 1951).

During either atrial or ventricular paroxysmal tachycardia, the murmurs of mitral stenosis are frequently absent Even in otherwise normal hearts the electrocardiograms during and for several days after an attack of paroxysmal tachycardia may show widened and inverted T waves and prolonged Q-T intervals in the limb leads (Smith, 1949)

Atrial Flutter. Atrial flutter is seen not nearly as commonly as atrial fibrillation; it is three times as common in males as in females and is more frequent in persons over 40 years of age. During atrial flutter, the atrial rate may vary between 200 and 400, averaging around 300 beats per minute, the ventricular rhythm is usually one-half of this and is regular. Atrial flutter may appear paroxysmally, lasting hours to days, or may be permanent; it is not affected by exercise, but pressure on the carotid sinus may halve the rate by producing a two-to-one or four-to-one block and the rate usually returns to normal or its preceding value on release of compression Recent studies suggest that the rhythm may be due to rapid impulse initiation from a unitary focus (Scherf *et al.*, 1948, Prinzmental *et al*, 1950). However, DiPalma and Schultz (1950) have reviewed in great detail the literature dealing with ectopic cardiac arrhythmias, and particularly that concerned with flutter and fibrillation, and have arrived at the opposite conclusion They believe that all such arrhythmias originate, not because some area

of the heart is hyperirritable, but rather because of the presence of one or more depressed areas having prolonged relatively refractory periods and even more prolonged conduction rates These areas of partial block, which may be very small, *allow re-entry of the impulse previously* generated by some other region or previously passed by the blocked area, and thus appear to become rapidly discharging foci They note that: (a) Ectopic impulses and flutter usually arise in the border of infarcted area, in the presence of myocardial disease, or when the myocardium is depressed as by chloroform or digitalis; (b) the ectopic impulse usually appears at an interval after the onset of the previous impulse which corresponds to that present during the "vulnerable period" (see page 181), and (c) if a hyperexcitable focus were responsible for ectopic tachycardias and flutter, the rhythm should frequently be only slightly faster than the normal sinoatrial rhythm, but this is never the case.

Digitalis may convert flutter to fibrillation and the rhythm may become irregular (Besoain-Santander *et al.*, 1950); the flutter may be converted occasionally to normal sinus rhythm (Tandowsky, 1945, *Tandowsky et al., 1946*). *Atrial flutter* can frequently be converted to normal sinus rhythm with quinidine (Tandowsky *et al.*, 1946, Sokolow and Edgar, 1950) Flutter, experimentally induced in dogs, may be converted to *fibrillation* by reflex excitation of the vagi induced by epinephrine; fibrillation is converted flutter under the vagal blocking effect of atropine (Scherf, 1949). The electrocardiogram usually shows the presence of a two-to-one atrioventricular conduction with relatively regular sinusoid atrial waves representing the atrial flutter. Even when the ventricular rhythm is irregular, the R-R intervals in the electrocardiogram tend to be grouped into regular intervals corresponding to multiples of the F-F intervals of the flutter frequency (Soderstrom, 1950).

Atrial Fibrillation. Atrial fibrillation is an irregularity in initiation of atrial impulse in which the atrial rate may be between 300 and 500 per minute, averaging around 400; the ventricular rate is usually around 130 to 150 per minute and is grossly irregular. The ventricular rate may vary slightly with excitement or emotion, is usually increased by exercise, is slowed by digitalis but it is not affected by amyl nitrite or atropine. The patient is usually conscious of the irregular cardiac action. The radial pulse rate is commonly less than the simultaneously-counted apical pulse rate because some of the ventricular beats fail to eject a sufficient volume of blood to produce a pulsation which will be transmitted to the periphery. The electrocardiogram frequently shows complete absence of P waves or only very fine oscillations. The QRS complexes are normal in appearance but irregularly spaced. The jugular vein pulsations usually show an absent *atrial wave (A wave), with two instead of* the normal three pulsations being present per ventricular beat.

The following theories have been advanced to account for initiation of the rapid impulse: (1) a rapid circus wave of irregular path is present (DiPalma and Schultz, 1950), (2) several centers of rapid formation of stimuli are active (Brams and Katz, 1931-32; Scherf *et al.*, 1950, Prinzmetal *et al*, 1950). *Atrial fibrillation*, like ventricular fibrillation, can be induced by a single electrical shock applied to the atrium in the "vulnerable period" during the relatively refractory phase of the atrial cycle (Orias *et al.*, 1950), it usually starts as a short series of accelerating premature beats (DiPalma and Schultz, 1950). Once atrial fibrillation starts, it usually persists throughout life unless stopped by administration of quinidine. *Atrial fibrillation is* most often associated with mitral stenosis

and is rarely seen with pure aortic valve lesions. Atrial fibrillation has been induced in dogs, subjected to hypothermia, by reflex excitation of the vagi by means of injection of epinephrine (Grant *et al*, 1949) Atrial fibrillation also occasionally occurs in man during digitalis administration (Katz, 1946). The effects of digitalis in the presence of atrial fibrillation are described on page 228.

The ventricular rhythm appears to be grossly irregular but, according to Soderstrom (1950), when large numbers of beats are measured the R-R intervals tend to be grouped into semiregular intervals corresponding to multiples of the refractory period of the atrioventricular nodal period. The upper limit of the R-R intervals corresponds to the spontaneous rhythm of the atrioventricular node. Variations of the observed R-R intervals from exact multiples of the nodal refractory period are attributed to variations in the atrioventricular conduction rate. The coronary blood flow tends to be reduced during atrial fibrillation, but the reduction is less than the corresponding decrease in cardiac output and aortic pressure. It is believed, therefore, that either the systolic extravascular compression of the coronary vessels or the coronary vasomotor tone is reduced (Wegria *et al.*, 1950a, b).

Ventricular Fibrillation. Ventricular fibrillation in man is almost invariably fatal. It represents the occurrence of a circus movement of excitation of the ventricles and if the heart is examined in an exposed chest it shows a wormlike movement and on palpation imparts a sensation like "a bag of worms." At the onset of ventricular fibrillation, the arterial blood pressure immediately falls to zero and respiration rapidly fails Ventricular fibrillation in man is usually a terminal event unless the process is stopped by "countershock" as noted below. However, at least one instance of transient recurrent attacks of ventricular fibrillation has been reported in a patient without organic heart disease (Moe, 1948). This patient experienced syncope during the attacks The electrocardiogram during ventricular fibrillation shows irregular wavelike movements of varying frequencies during the period of ventricular fibrillation

Ventricular fibrillation is initiated most commonly by coronary occlusion but also may be initiated during surgery of the heart by accidental mechanical or electrical excitation of the ventricle during early diastole, *i e*, during the "vulnerable" or relative "refractory period" (Wiggers, 1940, Moe *et al*, 1941, Hoff and Stansfield, 1949, Southworth *et al*, 1950) Ventricular fibrillation is also induced by the passage of an alternating electric current through the body, such as occurs during penal or accidental electrocution by high tension current

The "vulnerable period" probably coincides with the period of increased excitability which Suckling and co-workers (1950) noted in animals about 160 milliseconds after the onset of a previous excitation; the threshold for excitation appears to rise with intervals of 180 milliseconds and then falls to its lowest level with intervals of 230 or more milliseconds. DiPalma and Schultz (1950) believe that an area of partial block, caused by myocardial depression, is essential for the genesis of fibrillation. They believe that the basic mechanism is essentially similar to that in ectopic beats and flutter. If the heart can be exposed and subjected directly to a brief period of alternating current of the value of about 1.5 to 2.1 amperes, fibrillation can be stopped (Leeds *et al.*, 1951), probably because simultaneous excitation of all parts of the ventricle by the very strong current makes the entire ventricle refractory and thus prevents the spread o the circus movement of excitation.

Disturbances in Conduction of Impulse

Sinoatrial Block. Sinoatrial block is believed to occur when beats are suddenly dropped without other interruption in the rhythm, in other words, when the interval between two beats suddenly becomes twice the normal length. No other abnormality is seen in the electrocardiogram except the absence of the P wave and QRS-T complex at the moment of the dropped beat. This rather rare condition is considered to be due either to inability of the atrium to respond to the sinus beat or to some form of block existing temporarily between the sinoatrial node and the atrial tissue Causes which have been postulated are vagotonic state, arteriosclerotic heart disease and digitalis poisoning (Sabathie and Gaspary, 1947; Caviness, 1943)

Intra-atrial Block. Intra-atrial block has been described from electrocardiographic tracings only, it is characterized by the presence of broad, notched or prolonged P waves

Delayed Conduction (First Degree Block, Incomplete Block). Delayed conduction represents a slowing in the rate of propagation of the cardiac impulse from the atrium through the atrioventricular node and Purkinje system to the ventricle It can be detected only by the electrocardiogram or by jugular pulse tracings, and is characterized by a conduction time longer than 0 21 second, the upper limits of normal for adults with heart rates of around 70 The upper limits of normal shorten with decreasing age (0.19 second for ages 14 to 17 and 0.16 second for under one year, at heart rates of 70 per minute) and also with increasing heart rate (0.17 second for adults and 0.125 second for children, with heart rates of 130 or more per minute) (Ashman and Hull, 1941). Prolonged conduction is seen after administration of digitalis and in acute rheumatic fever. The latter is assumed to be due to damage to, or depression of, the atrioventricular node and the conduction tissue. P-Q intervals as long as 0 50 second may be seen. Apparently both atropine and Mecholyl may shorten the conduction time in the presence of delayed conduction (Messer *et al.*, 1949).

Prolonged Refractory Period (Dropped Beat, Second Degree Block, Partial Block). If for any reason the atrioventricular node and conduction tissue recover less rapidly than normally from a previous beat, *i.e.*, if the refractory period is prolonged, then the second impulse from the sinoatrial node may arrive at the atrioventricular node before it is fully recovered from the first. Under these conditions the second beat fails to get through and the ventricle does not respond until the third sinus beat, giving a two-to-one heart block. Such a condition may be detected by the electrocardiogram or by the registration of the jugular pulse. It may occasionally also be detected by auscultation of the heart, when normal first and second sounds will be heard and then, during the ensuing pause, an atrial beat may be heard without the customary first and second sounds, followed after an interval by a normal pair of heart sounds. The atrial beat will be observed to coincide with an atrial pulsation in the jugular vein. A prolonged refractory period may be seen with severe infections such as typhoid fever, diphtheria, influenza, scarlet fever and pneumonia, and myocardial damage resulting from coronary arterial disease. The ventricular rate may drop suddenly to as low as 30. Under certain conditions, a 4:3, 3:2 or 2.1 block may be noted. In these conditions there may be a combination of prolonged conduction and prolonged refractory periods.

Interference and Dissociation. Interference refers to failure of the second of two closely spaced impulses from the same or different sources to activate a portion

of the heart, owing to the normally long refractive state of heart tissue which follows its excitation by the first impulse. Dissociation denotes that the heart is activated first by one, then by another pacemaker. In both instances the refractory periods are assumed to be within normal limits, in contrast to block in which the refractory period is usually prolonged (Katz, 1946). The phenomena of interference and dissociation may lead to a number of complex arrhythmias. An example is the arrhythmia that occurs in the presence of nodal rhythm with retrograde block (which is normal) and a slower sinus rhythm. The sinus beats may occasionally fall in the nonrefractory period of the atrioventricular node and produce a beat of the ventricle. These forms of arrhythmia resemble those seen with atrioventricular block (Burchell, 1949).

Concealed Atrioventricular Conduction. Frequently a premature beat may be transmitted through the atrioventricular node (either forward or backward) and then be blocked before it excites the next chamber. The effect of the *concealed conduction* may be noted, however, by the prolongation of the next P-Q interval or failure of the next impulse from the pacemaker to be transmitted (Langendorf, 1948).

Complete Heart Block. Complete heart block is a condition characterized by a very slow ventricular rate which is independent of the atrial rate. It usually develops suddenly and may exist permanently thereafter. The ensuing idioventricular rhythm (see page 177) averages 30 per minute, it is independent of the atrial rhythm and is not affected by exercise, carotid sinus compression or atropine. The atria may even be fibrillating. In the electrocardiogram the ventricular complexes are normal. Auscultation may reveal atrial sounds occurring at a rhythm independent of the normal ventricular first and second sounds, and atrial pulsations (A waves) of the jugular vein may be noted which coincide with the atrial sounds and are independent of the two pulsations (C and V) produced by ventricular ejection and ventricular filling. Complete heart block is usually the result of myocardial damage owing to coronary artery disease or to severe infections such as influenza, typhoid fever, scarlet fever, diphtheria or pneumonia (Ide, 1950). Temporary periods of heart block have been noted during reflex vagal stimulation induced by massage of the carotid sinus (Schwartz and Eichna, 1950).

"Fusion" Beats. A beat of the atria or ventricles may be caused by two impulses arriving at the chambers so close together that only one beat results. Malinow and Langendorf (1948) have given a detailed classification of such fused beats and indicate that thay may arise (a) from two sources, *i.e.*, in the atria, from the sinoatrial and atrioventricular nodes or, in the ventricles, from the atrioventricular node and from an idioventricular beat, or (b) from one source such as that seen in the syndrome of the short P-Q interval and prolonged QRS complex.

Bundle Branch Block. Intraventricular Block. In bundle branch block the impulse is delayed in its spread through some part of the ventricles. This may occur as a result of injury to a portion of the specialized conduction tissue. The impulse has to be conducted by ordinary myocardial tissue past the area of block, following which it re-excites the more distal conduction tissue, allowing excitation of the remainder of the heart. The impulse is delayed during its spread through the ordinary myocardium so that the time required for excitation of both ventricles is longer than normal. The terms "intraventricular block" (Rosenman *et al.*, 1950) or "left- (or right-) sided retardation" (Rasmussen and Moe, 1948) have been suggested as preferable to "bundle branch block" in designating the condition of delayed conductio

in a portion of the ventricle. The latter authors found evidence of damage to the bundle in only 14 of 72 cases

Bundle branch block has been generally considered to indicate a grave prognosis However, in a recent survey of 100 cases of such block, 28 were found in patients under 40 years of age and seven in patients under 20 years of age. Twenty-nine of the 100 had no other evidence of organic heart disease, and many individuals were known to have had bundle branch block for at least 10 years. It has, therefore, been concluded that patients with bundle branch block have a much more favorable prognosis than heretofore considered (Langley *et al.*, 1947).

Pulsus Alternans. Pulsus alternans represents alternating strong and weak beats of the ventricles with a regular rhythm The alternations are usually noted on palpation of the pulse, registration of the arterial pressure pulses or arterial pressures, but alternation may also be seen in the amplitude of the QRS and ST complexes in the electrocardiogram (Katz, 1946, Groedel and Miller, 1949, Burch and Winsor, 1949; Hellerstein and Liebow, 1950). Ventricular alternation is seen most commonly with coronary artery disease and, as such, has a moderately serious prognosis. It is probably due to prolongation in the refractory period of part of the myocardial fibers which are rendered partially ischemic by the arterial disease (Figure IV-11). The prolonged refractory period of these tissues causes them to respond only to every other ventricular beat; the alternate beats are, therefore, weaker when some of the myocardial fibers fail to contract and stronger when all or the majority of them contract (Green, 1936).

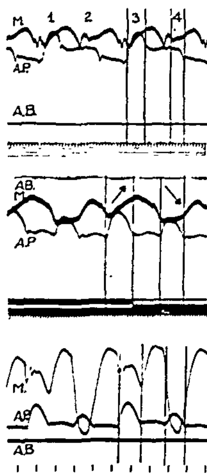


Figure IV-11. Three examples of pulsus alternans AP, aortic pressure, AB, base line for aortic pressure, M, myographic record Downward movement of the myographic record indicates lengthening, upward movement indicates shortening of the myocardial fibers In these studies the area of muscle, to which the myograph was attached, was rendered partially ischemic. Note the alternate large and small pulsations in the aortic pressure curve. The strong pulsations coincide with shortening, the weak pulsations with extension of the muscle fibers The rhythm is regular (Reproduced from Green, 1936).

General Comments. *Age.* Irregularities occurring before the tenth year usually represent sinus arrhythmias, although heart block and premature contraction may be seen, particularly accompanying enlargement of the heart. Atrial fibrillation rarely occurs before the age of 17. *Frequency.* The most common disturbance is atrial fibrillation which accounts for approximately 40 per cent of disturbances. Next most frequent are premature ventricular contractions which account for about 35 per cent of irregularities, and alternation for 10 per cent. Paroxysmal tachy-

cardia, heart block and flutter together make up the remaining 15 per cent of arrhythmias. At least 5 per cent of the irregularities are associated with cardiac failure

Heart rate. Heart rates of 35 and below usually indicate complete heart block Rates of 40 to 50 suggest prolonged refractory period. Rates of 130 and over, when persistent and associated with a regular rhythm, indicate tachycardia and rates of 120 and over, but with an irregular rhythm, usually represent atrial fibrillation. Atrial fibrillation is the most persistent. Other irregularities are usually transient (White, 1944).

TABLE IV-1

Differential Diagnosis of Cardiac Irregularities Based on Principal Clinical Signs

a. *Tachycardias*

Designation	*Rate Rhythm*	*Affected By*	*Course, Symptoms*	*Causes*	*Electrocardiogram*
Sinus	120-170, regular		Gradual onset and disappearance. Duration, minutes to days	Exertion, anoxia, emotion, atropine, *amyl nitrite, thy*roxin, hyperthermia, heart failure, shock and hemorrhage	P-Q low normal, QRS normal, Q-T *shortened*
Paroxysmal atrial. (Two to six times as frequent as ventricular)	120-200, usually 160-180, up to 300 in infants, very regular	May occasionally be stopped with exercise, carotid pressure, deep breathing and Mecholyl; does not vary with exercise Rate may remain slow after release of pressure May stop with *quinidine*	Sudden onset and disappearance Duration seconds to hours. May be unnoticed or associated with dyspnea May induce angina, fainting or mild heart failure	Unknown cause or exertion, fatigue, indigestion, infection, heart disease, use of tobacco, alcohol or digitalis	Rapid regular premature atrial beats, *i e*, inverted or diphasic waves, normal QRS or widened inverted T waves. Occa*sionally* 2 1 block or bundle branch block with very rapid rate
Ventricular (Rare, serious, active)	As in paroxysmal atrial May be slightly irregular	Digitalis contraindicated, may precipitate fibrillation	As in paroxysmal atrial	Often associated with organic heart disease	QRS resembles a premature beat, atria may beat independently or may fibrillate, or there may be backward conduction
Nodal atrioventricular (Very rare, active)	As in paroxysmal atrial but may be as slow as 90		As in paroxysmal atrial	As in paroxysmal atrial	Regular retrograde atrial response or absent P waves, QRST as for atrial tachycardia
Atrial flutter. (One fourteenth as common as atrial fibrillation)	Atrial rate 200 to 400, average 300 Ventricular rate usually one-half atrial rate, rhythm *usually regular*	Not affected by exercise, rest Pressure on carotid sinus may halve rate by caus*ing 2 1 block* or changing this to 4.1 block, with return to former rate on release of pressure. Digitalis may convert flutter to fibrillation Quinidine may convert to normal sinus rhythm	May be paroxysmal, last hours or years Symptoms depend on ventricular rate	Circus wave? More common in presence of heart disease. Three times as common *in males*. More frequent after age 40	Usually 2 1 A-V block May also be intraventricular block or complete A-V block. Regular rhythm. Oscillation of string, F waves, rather than distinct P waves
Atrial fibrillation, *see under c. Other Arrhythmias*					

TABLE IV-1, *continued*

b *Bradycardias*

Designation	*Rate Rhythm*	*Affected By*	*Course Symptoms*	*Causes*	*Electrocardiogram*
Sinus bradycardia	45 to 60			Occurs in sleep and in athletes Inhalation of irritant gas, pressure on eyeballs and carotid sinus, increased intracranial pressure, jaundice, epidemic parotitis, influ enza, excess of digitalis	Lengthening of P-Q, Q-T and Q-Q
Partial heart block. Dropped beats, second degree block	30 or more	Exercise or amyl nitrite may abolish	May appear suddenly May be associated with fainting Jugular pulse may reveal isolated atrial pulse waves Atrial heart sound may be present Sometimes Adams-Stokes syndrome	Digitalis, myocardial damage, severe infections, typhoid, diphtheria, influenza, scarlet fever, pneumonia, coronary artery disease	Ventricular rate may be faster with faster atrial rate (4 3, 3 2, 2 1 or 3 1 block may be present)
Atrio-ventricular nodal rhythm	30 to 50, average 40, but as high as 80, per minute, regular	May be returned to sinoatrial rhythm with atropine or exercise	Sometimes Adams-Stokes syndrome	Marked depression of sinoatrial node	P wave may be inverted, P-Q short, or P wave may follow QRS
Complete heart block, sinus standstill, idioventricular rhythm (passive)	Ventricular rate averages 30 per minute	Not affected by exercise	May appear suddenly May be associated with fainting Jugular pulse may have atrial waves Atrial heart sounds may be heard. Sometimes Adams-Stokes syndrome	Myocardial damage, severe infections, influenza, typhoid fever, scarlet fever, diphtheria, pneumonia, coronary artery disease	Atrial rate about 70, ventricular rate about 30 per minute Normal ventricular complexes

TABLE IV-1, *continued*

c. *Other Arrhythmias*

Designation	*Rate Rhythm*	*Affected By*	*Course Symptoms*	*Causes*	*Electrocardiogram*
Sinus arrhythmia	Normal rhythmic speeding and slowing with respiration	Abolished by exercise, atropine, hemorrhage (*i e*, on speeding of rate), contrary to atrial fibrillation	Normal	Normal	Normal
Premature atrial contractions	Normal		Usually none	Atrial myocardial anoxia, heart failure, rheumatic fever	Abnormal P wave inverted, or other abnormal shape, shorter preceding P-P interval than normal
Premature ventricular contractions	Normal		Prolonged pause	Ventricular myocardial anoxia, coronary artery disease	Abnormal QRS, prolonged, high voltage
Pulsus bigeminus	Normal		Usually none	Digitalis poisoning, re-entry rhythm	Second beat similar to premature ventricular beat
Pulsus alternans	Normal Rhythm regular		Alternate pulses are weaker than normal	Cardiac insufficiency plus prolonged refractory period of part of myocardial fibers	Rhythm regular Alternate beats may have lower voltage
Atrial fibrillation	Atrial rate 300 to 500, average 400. Ventricular rhythm irregular, 130-150 per minute	May vary with excitement and emotion Digitalis slows heart by increasing A-V block. Amyl nitrite, exercise and atropine abolish arrhythmias of sinus origin but not those due to fibrillation Quinidine frequently converts to normal sinus rhythm	Patient conscious of irregular heart action, palpitation. Rhythm grossly irregular. Pulse deficit. Absence of presystolic mitral murmur and absence of triple jugular venous pulse	Circus movement, commonly associated with heart disease, especially mitral valve disease. Two or three times as common in males	Absence of P waves or very fine P waves present. QRS normal but irregularly spaced
Ventricular fibrillation		May be abolished by immediate massage and "countershock"	Arterial pressure falls to zero, respiration stops. Most common cause of sudden death	Coronary occlusion. Electric shock	Fine wave-like undulations. Absence of QRS-T complexes

TABLE IV-1, *continued* *d* *Abnormalities Diagnosed Only by Electrocardiogram*

Designation	*Rate, Rhythm*	*Affected By*	*Course Symptoms*	*Causes*	*Electrocardiogram*
Prolonged conduction. First degree block, incomplete block	Normal		May be shortened by atropine	Digitalis, rheumatic fever, damage to A-V node and conduction tissue	P-R interval 0 21 to 0 50 second
Interpolated extrasystoles	Normal			Likely to occur only with relatively slow atrial rate	Ventricular premature beat placed so that refractory period is over before next atrial beat
Bundle branch, intraventricular block	Normal		Usually permanent	Damage to one bundle branch	All ventricular beats resemble premature beats in appearance, *i.e.*, higher voltage and prolonged duration
Wolff-Parkinson-White syndrome (fusion beats)	Normal		(Paroxysmal tachycardia may be mistaken for this syndrome)	Congenital origin, bundle of Kent	Short P-Q with prolonged QRS
Sinoatrial block	Normal except for missing beats		No symptoms	Vagotonic state, arteriosclerotic *heart disease, digitalis* poisoning	Occasional absence of P and QRS-T
Intra-atrial block	Normal			Coronary artery disease?	P waves broad, notched or prolonged

2. STRUCTURAL DEFORMITIES OF HEART

Acquired Valvular Defects

Mechanisms for Production of Murmurs. Murmurs are primarily caused by vibrations of the cardiac and vascular structures set up by eddy currents in the blood In a tube of a given size, eddy currents develop whenever the velocity of flow exceeds, or the viscosity drops below, a critical figure. Increase in the diameter of a vessel, for a given viscosity and mean velocity, increases the likelihood of eddy currents Eddy currents develop at lower velocities of flow whenever sudden dilations of the tube, or bends or angulations occur. The cardiovascular system is so constructed that it normally operates just below the critical level for the production of eddy currents (Green, 1950). Slight increases in velocity of flow or abnormalities in the structure of the heart or vessels such as narrowing of the exit tract or regurgitation or decrease in viscosity will, therefore, produce murmurs of varying intensity, depending upon the vigor of the eddy currents induced

Grading of Murmurs. For convenience in following changes in cardiac lesions and in interpreting their significance, many clinicians grade the loudness of murmurs. Levine (1933) has graded a murmur 1+ if it can just be heard after careful auscultation, and 6+, the loudest possible murmur, which can usually be heard with the unaided ear at some distance from the chest. Murmurs between these extremes are graded 2+ to 5+. He believes that murmurs graded 2+, 3+ and louder are usually caused by structural disturbances of the valves, heart or blood vessels, bu

occasionally may be unexplained at autopsy White and associates (1949) indicate that, in Boston, murmurs are graded on a basis of 1 to 5. In my own institution, a similar scale is employed (McMillan and Sawyer, 1951) as follows: grade 1, very slight, difficult to hear with careful auscultation, grade 2, faint, but heard without difficulty over a relatively small area of the chest, grade 3, moderate, heard quickly and easily and over an area of several centimeters of chest wall, grade 4, loud, impressing the examiner with its loudness as soon as auscultation is begun and may be audible over much of the precordium or well into the axilla, grade 5, very loud, audible with unaided ear or with stethoscope not in contact with the chest wall On the basis of a follow-up of rejectees from World War II, White and associates (1949) report that "slight (grade 2) systolic murmurs at the apex are borderline and open to careful scrutiny, as is also true of systolic murmurs of moderate intensity (grade 3) at the pulmonary valve area, especially when the pulmonary second sound is unduly accentuated. Aortic systolic murmurs . . . doubtless should be considered abnormal when more than very slight (grade 1) in intensity. Diastolic murmurs anywhere were adjudged abnormal"

Classification of Murmurs. White and associates (1942) propose that murmurs be divided into physiologic and pathologic types. Under *physiologic murmurs* they group (1) *intracardiac and intravascular* murmurs, *i.e.*, those systolic murmurs heard over the pulmonic and apical areas which are evanescent, short, soft and blowing, and heard over a limited area (grade 1), not associated with other evidence of cardiac disease, and varying with position and activity, being loudest and often heard only in recumbency and after exertion, (2) *extracardiac* murmurs, including sounds originating in the lungs — the cardiorespiratory murmurs and pericardial sounds.

Among *pathologic murmurs* these authors include those which are caused by (1) *structural disease of the valves*, (2) *congenital cardiovascular defects*, (3) *dilation of a cardiac chamber or blood vessel* which may be secondary to cardiovascular disease such as hypertension, anemia or rheumatic myocarditis, and (4) *acute pericarditis.*

According to Levine and Harvey (1949), nonsignificant functional (physiologic) systolic murmurs commonly occur in anemia owing to the accompanying increased cardiac output and resulting higher velocity of flow, and the concomitant reduction in viscosity of the blood Murmurs may also be heard during fever, hyperthyroidism and exercise; tachycardia may occasionally bring out systolic murmurs and at other times suppress them It is probable that these murmurs are caused primarily by the increased velocity of blood flow associated with these conditions They believe that, in the absence of fever, tachycardia, hyperthyroidism and anemia, a grade-2 apical systolic murmur is more likely produced by an organic mitral insufficiency than by physiologic causes. Master (1948) believes that a history of rheumatic fever or of an infection with a hemolytic streptococcus, in a patient having a loud apical systolic murmur, should be accepted as almost certain evidence of disease of the mitral valve

Frequency of Occurrence of the Various Types of Valvular Lesions. The following table gives the frequency of occurrence of valvular lesions as noted by White (1944).

These lesions are discussed in detail in Chapter V on Congenital Malformations, in Chapter VIII on Rheumatic Disease, and also in Chapter XIII on Clinicopathologic Correlations. The discussion in this section will be concerned principally with the physiologic effects of these lesions. In order to simplify the presentation, insuffi-

Valve	Occurrence as Single Valve Lesion	Total Occurrence
	%	%
Mitral	52	83
Aortic	13	44
Tricuspid	3	16
Pulmonic	0	2
	68	
Mitral and aortic	19	
Mitral, aortic and tricuspid	11	
Pulmonary and tricuspid	1	
All four valves	1	
	100	

ciency and stenosis will be discussed separately for each of the valves. The physiologic effects of multiple lesions will usually be the sum of those of the individual valvular defects.

Aortic Valvular Disease. *Aortic insufficiency.* Aortic insufficiency is seen principally in syphilitic or rheumatic disease of the aortic valve, occasionally in calcific sclerosis (Fenichel, 1950), and rarely following rupture of the valve by physical trauma or as a result of severe exercise in a valve already damaged by disease As a consequence of the failure of the aortic valve to close properly, blood regurgitates into the ventricle during ventricular diastole. The volume of blood regurgitating may be as much as 50 per cent of the preceding systolic discharge. If the heart is able to maintain compensation, the systolic discharge will equal the normal systolic discharge plus that which regurgitates with each diastole. With regurgitation of 50 per cent of ejected blood, the stroke volume must be twice normal to maintain a normal rate of circulation through the body.

The regurgitant fluid added to the volume of blood entering the ventricle from the atrium causes a greater initial ventricular volume and tension, and thereby a stronger ventricular systole and a larger systolic discharge. As a consequence of the greater initial length of the ventricular myocardial fibers, there is a more rapid rise in tension in the ventricle during isometric contraction The greater force of ejection and the lower aortic diastolic pressure allow the heart to produce a more rapid, earlier and more complete ejection of blood into the aorta and a sharper rise in aortic pressure The sharply-rising wave front in aortic pressure is transmitted to the periphery as a water-hammer pulse, giving rise to a tap felt by the palpating hand and to the pistol-shot pulse heard at the inguinal canal, and to the higher systolic pressure recorded with the sphygmomanometer More blood is ejected during the early part of systole than is normal and, as a consequence, the pressure in the ventricle and aorta begins to drop rather rapidly during the latter part of ventricular systole This produces the early decline noted in the peripheral pulse The regurgitation of blood into the ventricle together with the normal flow of blood into the capillaries causes a greater drop in pressure in the aorta during diastole and, therefore, a lower diastolic pressure. The wide oscillation in pressure in the aorta causes sufficient fluctuation in the flow of blood into the capillaries to produce a rhythmic variation in color of nailbed, this is designated the *capillary pulse* Electrokymographic studies of the aortic pulsations demonstrate a rapid diastolic decline in volume with diminution or absence of the normal postincisural increase in volume Records from the left ventricle show that systole is slightly prolonged, and that ventricular filling begins at the onset of protodiastole instead of the end of isometric relaxation (Heyer *et al*, 1950).

The stream of blood regurgitating through the aortic valves which are tense, light in weight and short in length sets up high-pitched vibrations which are heard best with the diaphragm-type of stethoscope in the third left intercostal space.

The sounds may be intensified by directing the patient to lean well forward and hold his breath after full expiration in order to bring the chest wall as close as possible to the ascending arch of the aorta. Possibly because of partial closure of the mitral valve by the regurgitating aortic stream and possibly also because of enlargement of the left ventricle, eddy currents* are frequently set up in the stream of blood passing from the left atrium to the ventricle during ventricular diastole, giving rise to a murmur which mimics that of mitral stenosis. This "false" murmur is called the Austin Flint murmur.

As a consequence of the increased initial ventricular volume and initial length of the myocardial fibers the heart hypertrophies and compensates for the load. If the increase in this load is excessive, however, heart failure may occur (see section on Heart Failure, page 232). With excessive dilatation of the ventricle, the mitral ring may become dilated leading to mitral insufficiency, this condition plus the excessive rise in ventricular diastolic pressure may lead in turn to elevation of pulmonary arterial pressure and ultimately to right ventricular dilatation and failure

Aortic stenosis. Stenosis of the orifice of the aortic valve is seen with rheumatic disease and in calcific sclerosis of the aortic valve, and may also be present as a congenital anomaly. It is frequently accompanied by aortic insufficiency. The opening must be reduced to from one-half to one-quarter of the normal to cause significant symptoms. The narrow opening increases the resistance to ejection by the ventricle. The blood thus retained within the ventricular cavity, combined with the normal inflow from the atrium, leads first to ventricular dilatation and then to a steeper rise of pressure during isometric contraction and to development of sufficient pressure to eject the normal quantity of blood through the narrowed opening. The passage of the blood through the narrowed opening into the wider aorta sets up eddy currents which give rise to a thrill and to a loud systolic murmur which may be observed in the second right intercostal space and often up into the neck. The entrance of blood into the aorta is less rapid than normal and the pulse shows a correspondingly slow rise. As a consequence of the dilatation, hypertrophy of the ventricular wall ensues. If this is sufficient to maintain a normal minute volume of circulation, compensation is maintained; but if output fails to be maintained within normal range, further dilatation, hypertrophy and eventual cardiac failure may be noted as described above under Aortic Insufficiency and below under Heart Failure.

Coronary circulation is impaired during systole with aortic stenosis and during diastole with aortic insufficiency. Pulsus alternans and premature systoles may be observed in these conditions. The electrocardiographic changes recorded with aortic insufficiency and aortic stenosis are those associated with left ventricular hypertrophy.

Mitral Valvular Disease. *Mitral insufficiency.* Mitral insufficiency is usually caused by rheumatic disease and is almost always associated with some degree of stenosis. A functional or relative insufficiency may, however, result from dilatation of the mitral ring by left ventricular dilatation, as in aortic insufficiency or stenosis, myocardial infarction, anemia or adhesive pericarditis (Levine and Harvey, 1949). During ventricular systole, blood is regurgitated into the atrium. During ventricular diastole this volume of regurgitated blood is added to the venous blood normally returned, thus increasing the ventricular diastolic size and tension. The latter releases the extra energy required by the

* Eddy currents are likely to occur whenever fluids flow rapidly past abrupt turns, or through a narrow passage into a cavity of larger diameter.

ventricle and leads to a small degree of left ventricular dilatation and hypertrophy The greater volume of blood in the atrium leads likewise to atrial dilation and hypertrophy of mild degree. Atrial pressure rises slightly but if there is minimal associated mitral stenosis the atrium is able to empty relatively readily and the average pressure in the atrium is, therefore, only slightly above normal and the pulmonary capillary pressure inappreciably elevated. The flow of blood from ventricle to atrium through the narrow orifice into the larger atrial space gives rise to a systolic murmur of medium pitch which is frequently transmitted well out into the axilla Mitral insufficiency may develop suddenly as a result of rupture of a papillary muscle which is involved by infarction. When this occurs, a harsh systolic murmur is heard, and there is often associated pain and profound shock (Smith, 1950) Gorlin and Dexter (1951) have attempted to calculate the effective cross-sectional area of the insufficient mitral valve from simultaneous measurements of pulmonary capillary and brachial arterial pressures and cardiac output. Draper and associates (1951) found, as with mitral stenosis (below), that cardiac output may not increase adequately with exercise, the arteriovenous difference in oxygen concentration was increased at rest and greatly increased with exercise. These effects were even more marked with mitral insufficiency than with mitral stenosis. However, the right ventricle was not significantly enlarged unless there was actual heart failure.

Mitral stenosis Stenosis of the orifice of the mitral valve is most commonly seen in rheumatic disease. The narrow opening interferes with the entrance of blood from the atrium into the ventricle and causes eddy currents to form during ventricular filling which, because of the large mass and looseness of the mitral valves at this time, gives rise to a low-pitched rumbling murmur. This murmur occurs during the period of rapid ventricular filling in mid-diastole and is accentuated in late diastole during atrial systole, when a second rush of blood from atrium to ventricle occurs The murmur is heard best in the apical region with the patient lying on his left side and is accentuated by exercise or other factors which increase the cardiac output The first sound is accentuated in the presence of mitral stenosis, giving rise to a snapping sound, this change in character may be noted even in the absence of audible murmurs (Levine and Harvey, 1949). However in contrast, the first sound may occasionally have a crescendo character resembling the presystolic murmur of mitral stenosis, yet phonocardiograms may show that the sounds all begin after the Q wave of the electrocardiogram (Alimurung *et al*, 1949) For discussion of the mechanisms leading to intensification of the first heart sound, see page 140 Occasionally a third sound, called by some writers the "opening snap," may be heard at the apex in patients with mitral stenosis, even in the absence of murmurs. It should be distinguished from gallop rhythm (Levine and Harvey, 1949). The exact cause of the sound is not known.

Because of the resistance to emptying of the atrium, it becomes distended and hypertrophied, and atrial pressure tends to remain continuously elevated. This gives rise in turn to an elevation of pulmonary capillary and pulmonary arterial pressure (Dexter *et al*, 1950; Gorlin *et al*, 1951) and frequently to right ventricular dilatation and hypertrophy. The cardic output tends to be below normal at rest and fails to rise normally with exercise. The arteriovenous difference in oxygen concentration is elevated at rest and increases abnormally with exercise (Draper *et al*, 1951; Gorlin *et al*, 1951).

The roentgenogram shows the pr[illegible] [illegible]ase in the shadow of t[illegible]

ventricular infundibulum and pulmonary trunk and well marked enlargement of the left atrial shadow which in the oblique position fills the clear space normally seen along the esophageal shadow. The right ventricle is usually not enlarged except in the presence of heart failure (Draper *et al.*, 1951). Gorlin and Gorlin (1951) have derived a formula by which they believe they can calculate the effective cross-sectional area of the normal or stenotic valve from measurements of pulmonary "capillary" pressure and cardiac output.

Atrial fibrillation frequently accompanies mitral stenosis, in which case the presystolic murmur (caused by atrial systole) is absent The electrocardiogram may show increased amplitude of the P waves, QRS deflections characteristic of right ventricular hypertrophy, and atrial fibrillation when this is present. The pulmonic second sound is frequently accentuated. The late complications of this lesion are pulmonary congestion and right ventricular failure as described in the section on Heart Failure (page 232) and systemic arterial embolism from detachment of mural thrombi (Jordan *et al*, 1951).

Pulmonary Valvular Disease. *Pulmonary insufficiency.* Pulmonary valvular insufficiency is almost always functional (*i e*, due to dilatation of the pulmonary valve ring), secondary to pulmonary arterial hypertension from any cause, though it may occur as a terminal event in subacute bacterial endocarditis. The regurgitation produces a blowing, early diastolic murmur heard along the left sternal margin and leads to dilatation and hypertrophy of the right ventricle. Fluoroscopic examination reveals active pulsation of the pulmonary trunk and right ventricle. The electrocardiogram reveals right ventricular hypertrophy unless masked by concomitant hypertrophy of the left ventricle.

Pulmonary stenosis. Stenosis of the orifice of pulmonary valve or trunk is usually congenital and associated with other abnormalities. The stream of blood leaving the right ventricle sets up vigorous eddy currents as it passes through the stenotic orifice into the pulmonary trunk, giving rise to a harsh systolic murmur and a thrill in the second left intercostal space. The increased resistance to right ventricular ejection leads to incomplete emptying with resulting dilatation and hypertrophy of the right ventricle and, if severe, also of the right atrium. Fluoroscopic examination reveals the enlarged chambers and decreased pulsation of the pulmonary vessels. The electrocardiogram is characteristic of right ventricular hypertrophy The patient usually suffers from stagnant anoxia (see page 220) due to the slow rate of circulation of blood and this may lead to cyanosis. Dyspnea is common. Catheterization of the pulmonary trunk and right ventricle with registration of the pressure reveals a greater pressure in the ventricle than in the pulmonary trunk during systole (Cournand *et al.*, 1949, Dow *et al*, 1950).

Tricuspid Valvular Disease. *Tricuspid insufficiency.* Deformity of this valve is rare and, when seen, is usually associated with mitral valvular disease which overshadows it Rheumatic infection, when it damages this valve, usually leads to combined stenosis and insufficiency. Functional insufficiency may be seen with right ventricular dilatation in heart failure. Tricuspid insufficiency increases the work load on the right atrium and ventricle, in a manner similar to the effects of mitral insufficiency on the left chambers. The regurgitant stream, flowing during ventricular systole through the narrow orifice into the larger atrium, sets up eddy currents which give rise to a murmur heard best over the lower end of the sternum. This murmur is accompanied by an exaggerated prolonged positive systolic wave in the jugular pulse or in records of pressure obtained during right atrial catheteri-

zation — instead of the normal negative wave (Messer *et al.*, 1950) — by a pulsation in the superior vena cava which can be seen during fluoroscopic examination, and by pulsation of the liver. All of these closely follow the first heart sound

Tricuspid stenosis. Tricuspid stenosis induces eddy currents during the phase of rapid ventricular filling and, therefore, produces low-pitched murmurs in mid-diastole and during atrial systole which are most readily heard over the lower end of the sternum. If tricuspid stenosis is present alone, no evidence of either left or right ventricular hypertrophy will be found but the right atrium will be dilated and hypertrophied and the systemic venous and right atrial pressures will be elevated Associated with the latter there may be a strong atrial (*a* wave) pulsation in the jugular and atrial pulses (Vesell, 1949), a presystole pulsation in the liver and a prominent P wave in the electrocardiogram

Right-Sided Failure Caused by Encroachment of Hypertrophied Left Ventricle upon the Right Ventricular Cavity. Bernheim's Syndrome. In this syndrome marked dilatation and hypertrophy of the left ventricle occurs. The ventricular septum bulges into the right ventricular cavity forming a barrier to the flow of blood into the right ventricle. The latter leads to marked hypertrophy and dilatation of the right atrium. Systemic engorgement occurs early, pulmonary congestion is noted only terminally (Atlas *et al.*, 1950, Russek and Zohman, 1950). Evans and White (1948), however, doubt that the above phenomena represents a true syndrome

Congenital Defects

Congenital defects are discussed in detail in Chapter V. Taussig (1947) has classified congenital defects into two groups: (a) those which deprive the body of an adequate amount of oxygenated blood and (b) those which permit the body to receive an oxygen supply sufficient for the growth of the individual. The former are usually associated with varying degrees of cyanosis. The following discussion will be limited to a consideration of the mechanisms producing cyanosis.

Mechanisms Producing Cyanosis. *Average quantity of reduced hemoglobin in the capillary blood necessary to cause cyanosis* According to Lundsgaard and Van Slyke (1923), visible cyanosis, that is a purplish or plum-colored discoloration of the skin, is seen whenever the average cutaneous capillary blood contains 5 grams of reduced hemoglobin per 100 ml. of blood. Assuming that 1 gram of hemoglobin transports 1 33 ml. of oxygen, the concentration of reduced hemoglobin can be expressed in terms of equivalent milliliters of reduced hemoglobin per 100 ml of blood. Accordingly, cyanosis would be seen whenever the blood contains $5 \times 1.33 = 6.7$ equivalent volumes of reduced hemoglobin per 100 ml of blood.

Normal average capillary content of reduced hemoglobin In normal persons with 15 grams of hemoglobin per 100 ml of blood the capacity of the blood when fully saturated would be 20 ml of oxygen per 100 ml of blood. The arterial blood will be 94 to 97 per cent saturated normally and will contain, therefore, about 19 ml. of oxygen per 100 ml. blood and 1 equivalent ml of reduced hemoglobin per 100 ml of blood. During its passage through the capillaries the blood will give up approximately 5 ml of oxygen per 100 ml. of blood and the venous blood will, therefore, have approximately 6 equivalent ml. of reduced hemoglobin ($1 + 5 = 6$ ml. per 100 ml blood), and 14 ml. of oxygen carried by the oxygenated hemoglobin The average capillary content of reduced hemoglobin will be $\frac{1+6}{2} = 3.5$ equivalent ml. per 100 ml. blood, *i e.,* well under the amount necessary to cause cyanosis.

Effect of the quantity of blood in the capillaries on the production of cyanosis. By constricting the efferent veins or dilating the cutaneous capillaries and venous plexus, it is possible to increase the quantity of blood in the skin, even though the rate of blood flow, the oxygen utilization, and the average quantity of reduced hemoglobin per 100 ml of capillary blood be unchanged If under these circumstances the quantity of blood in the skin is doubled, the quantity of reduced hemoglobin per unit area of skin will be doubled and cyanosis will result

Effect of increased cutaneous oxygen consumption on oxygen utilization and on average capillary content of reduced hemoglobin Oxygen utilization is defined as the amount of oxygen removed from each 100 ml. of blood flowing through the tissues. If the rate of uptake of oxygen by the tissues is augmented without a rise in the blood flow, there will be a proportional increase in the oxygen utilization and in the average amount of reduced hemoglobin in the cutaneous capillaries If the oxygen utilization is augmented to 12 ml. per 100 ml. of blood flow, or to 2.4 times the normal, the average capillary blood will contain $\frac{1+13}{2} = 7$ equivalent ml. of reduced hemoglobin or enough to produce cyanosis that is just detectable.

Effect of cutaneous blood flow on oxygen utilization and average capillary content of reduced hemoglobin. With no change in either the rate of oxygen consumption by the tissues or the quantity of blood in the cutaneous capillaries at any instant, a reduction in the rate of blood flow in the skin will also increase the oxygen utilization, *i e.*, the amount of oxygen removed per 100 ml. of blood flow. The cutaneous blood flow would have to be reduced to $\frac{5}{12} = 0.42$ of the normal rate in order to increase the oxygen utilization to the 12 ml. per 100 ml. necessary to cause cyanosis $\left(\frac{1+13}{2} = 7\right)$.

Effect of admixture of venous blood with arterial blood in the aorta. If for any reason a mixture of arterial and venous blood enters the aorta, the content of reduced hemoglobin in the blood circulating in the arteries will be increased. If the concentration of hemoglobin, the rate of flow, and the oxygen consumption of the tissues are all unchanged, the quantity of reduced hemoglobin in the veins and the average content in the cutaneous capillaries will both be increased by such admixture of venous blood. The minimum amount of reduced hemoglobin which must be present in this mixture of blood when cyanosis is detectable can be computed as follows. Let X equal the content of reduced hemoglobin in the aortic blood necessary to cause such cyanosis If we assume an oxygen utilization of 5 ml /100 ml., then, since cyanosis will be produced by an average capillary content of reduced hemoglobin of 7 equivalent ml. per 100 ml of blood:

$$\frac{X + (X+5)}{2} = 7$$

and $X = 7 - 2.5 = 4.5$ equivalent ml. of reduced hemoglobin per 100 ml. in the arterial blood. The venous blood will then have $4.5 + 5 = 9.5$ equivalent ml. of reduced hemoglobin per 100 ml. The minimum amount of such venous blood that would have to be mixed with oxygenated blood containing 1 equivalent ml. of reduced hemoglobin per 100 ml. to produce cyanosis can then be calculated as follows:

Let Y equal the fraction of venous blood that is to pass directly from the right atrium or ventricle to the aorta. Then 1 minus Y will equal the fraction that will flow through the lungs. Then:

$$Y \times 9.5 + (1 - Y) \times 1 = 4.5$$
$$Y = 0.41$$

Thus if 0.41 of this venous blood passes directly into the systemic arterial circuit

and 0.59 goes through the lungs, cyanosis will be just detectable. The blood in the arteries would be $\frac{15.5}{20} \times 100 = 78$ per cent saturated with oxygen. Apparently through an error in mathematics, Taussig (1947) concluded that cyanosis could be produced by admixture of as little as 20 per cent of venous blood with the oxygenated blood.

Effect of polycythemia Cyanosis very frequently accompanies polycythemia especially when the oxygen capacity of the blood is more than 23.5 ml per 100 ml Increasing the content of hemoglobin in the blood usually results in the blood being less completely oxygenated during its passage through the lungs If we assume that only the normal 19 ml. of oxygen were taken up by each 100 ml. of blood flowing through the lungs, the minimum concentration of hemoglobin that would be necessary to cause cyanosis would be 17.7 Gm. per 100 ml. of blood This would give the blood an oxygen capacity of 23.5 ml per 100 ml. and the arterial blood would contain reduced hemoglobin in the amount of $23.5 - 19 = 4.5$ equivalent ml./100 ml As in the case of admixture of venous blood, this would give an average capillary content of reduced hemoglobin of $\frac{4.5 + 9.5}{2} = 7.0$ equivalent ml./100 ml., just sufficient to cause cyanosis Under such assumed conditions the arterial blood would be $\frac{19}{23.5} \times 100 = 81$ per cent saturated with oxygen. In actual conditions the arterial blood would probably take up more than 19 ml of oxygen per 100 ml. of blood but at the same time the blood volume and the quantity of blood in the cutaneous capillaries is increased in polycythemia, thus making the degree of arterial unsaturation more apparent

Effect of anemia. Cyanosis is rarely seen *in anemia and practically never when the* oxygen capacity of the blood is less than 3 ml per 100 ml If the hemoglobin concentration were reduced just to 9.8 Gm./100 ml of blood (oxygen capacity = 13 ml./100 ml.) and if the blood flow were slow enough so that all the oxygen was *removed from the blood during its passage* through the cutaneous capillaries and if the arterial blood maintained the normal equivalent ml./100 ml. of reduced hemoglobin, then the average capillary content of reduced hemoglobin would be $\frac{1 + 13}{2} = 7$ equivalent ml., *i.e.*, just sufficient to cause cyanosis Cyanosis would be almost impossible with anemias of more severe degree, and unlikely even at this degree, since in anemia it is unlikely that there would be as much as 1 equivalent ml. of reduced hemoglobin per 100 ml. of arterial blood and since the oxygen utilization would never be 100 per cent Cyanosis also would be unlikely because the blood volume and the content of the blood in the cutaneous capillaries is less than normal in anemia.

Phenomena associated with cyanosis Whenever cyanosis is present for any length of time, clubbing of the fingers and toes is usually seen Absence of clubbing usually means that the cyanosis is of recent origin The clubbing represents an overproduction of capillaries, dilatation and thickening of the blood vessel walls, an increase in connective tissue and, when marked, thickening of the periosteum The cause of its production is uncertain since it may occur with some diseases of the gastrointestinal system in the absence of anoxia (Wiggers, 1949, p. 486). Clubbing is rarely seen in association with congenital heart disease, except when cyanosis is present Cyanosis due to congenital heart disease is usually also associated with a shortened arm-to-tongue circulation time due to the presence of a right-to-left shunt

3. DISTURBANCES OF CORONARY CIRCULATION

Relative Insufficiency of Coronary Circulation. Angina Pectoris

The term *relative coronary insufficiency* may be applied to any condition in which the coronary blood flow is not interrupted but is reduced below the immediate demands of any area of the myocardium. Such insufficiency is usually present for only a few seconds to minutes and ordinarily the associated disturbances are rapidly reversible upon relief of the state of insufficiency. According to White (1944), the average duration from the first symptom to death in a series of 445 patients who were having definite attacks of angina was 7 9 years. Fifty-two of these patients had lived an average of 18.4 years up to the date of the report Boas (1951) calculated that the average duration of life in 124 patients with coronary artery disease, who have been under observation for 10 years or more, was 13 6 years from onset of symptoms to death. The prognosis was better in those having an onset with angina than in those having an onset with infarction.

Hecht (1949) suggests the terms *myocardial ischemia without tissue destruction* for angina and *myocardial ischemia with tissue destruction* for coronary occlusion. However, tissue destruction can result from relative myocardial ischemia without occlusion, while coronary occlusion may not result in tissue destruction if there is adequate existing collateral circulation or if the patient dies soon after the onset of the attack (Wang *et al.*, 1948).

FACTORS LEADING TO CORONARY INSUFFICIENCY

Narrowing of the Coronary Arteries. As described in Chapter VII the most common cause of narrowing of the coronary vessels is atherosclerosis (Horn and Finkelstein, 1940, Wartman, 1940). Mann and associates (1938) believed that the lumen of a carotid artery could be reduced by 50 to 70 per cent without affecting the volumetric rate of flow. Shipley and Gregg (1944), however, considered that the effects of the constriction increased with the length of the narrowed portion, with the viscosity of the blood, with the rate of flow, and with the reciprocal of the resistance to flow in the terminal vessels beyond the area of constriction.

Resistance to flow. With a given arterial pressure the rate of flow is dependent upon the sum of the resistances to flow in the arteries, arterioles, capillaries and veins, which, in electrical terminology, are arranged in series. Resistance can be expressed simply as the drop in pressure along the segment, divided by the rate of flow, *i.e.*, in mm Hg/ml./min. A convenient unit for resistance is the peripheral resistance unit (PRU) = 1 mm. Hg/ 1 ml./min. (Green *et al*, 1944; Green, 1950), it has the same significance as the ohm in electrical terminology.

Effect of narrowing a coronary artery when the coronary arterioles are constricted, i e., when cardiac work is minimal. With the subject resting and the cardiac work at a basal level, the coronary arterioles are constricted and the resistance to flow through them is high. For example, in the case of an artery which supplies blood to 100 Gm. of myocardium, the resistance to flow through the associated arterioles, capillaries and veins may be of the order of $\frac{99 \text{ mm Hg}}{80 \text{ ml./min.}} = 1.24$ PRU. The resistance to flow in the artery itself will be very low, of the order of $\frac{1 \text{ mm. Hg}}{80 \text{ ml./min.}}$ $= 0.013$ PRU, and the total resistance (aorta to coronary sinus will be: $0.013 + 1\ 24 = 1.253$ PRU. With an aortic pressure of 100 mm. Hg (coronary sinus pressure as-

sumed to be zero), the normal flow would be $\frac{100}{1.253} = 80$ ml./min. Flow $= \frac{\text{pressure}}{\text{resistance}}$ this is quite comparable to the equation used in electricity: amperes (rate of flow of current) $= \frac{\text{volts (electrical pressure)}}{\text{ohms (resistance)}}$

If under resting conditions the coronary artery were narrowed sufficiently to increase its resistance to flow 45-fold, *i.e.*, to 0.6 PRU, the total resistance would be elevated only to $0.6 + 1.24 = 1.84$ PRU With the same aortic pressure used above *i.e.*, 100 mm Hg, the flow would be $\frac{100}{1.84}$ $= 54$ ml./min. or 68 per cent of the normal.

Effect of narrowing a coronary artery when the coronary arterioles are dilated, i.e., when cardiac work is maximal During exercise the cardiac work is increased and the coronary arterioles dilate. If, in the above example, the maximum dilation of the arterioles is such that the resistance to flow through the arterioles, capillaries and veins is reduced 4-fold,* *i.e.*, to 0.31, then, in the normal heart the total resistance would be $0.013 + 0.31 = 0.323$ PRU. At an aortic pressure of 100 mm. Hg, the coronary flow would be $\frac{100}{0.323} = 310$ ml./min. Narrowing the artery to the same extent as indicated above would cause the total resistanec to be $0.06 + 0.31 = 0.91$ PRU and the flow would be $\frac{100}{0.91} = 110$ ml./min. This equals $\frac{110}{310} \times 100 = 35$ per cent of the expected flow, as compared to 68 per cent with the arterioles constricted. Thus we see that narrowing of a large artery influences flow in inverse proportion to the degree of arteriolar constriction

Compensatory arteriolar dilation in response to narrowing of a coronary artery. We may look at the effect of constriction of a coronary artery in another way. Let us assume that in a subject at rest the main coronary artery is narrowed sufficiently to reduce the flow to 68 per cent of normal (example 2 mentioned above). Compensatory dilation of the arterioles will now occur tending to restore the total resistance and, therefore, the flow towards normal In the example above (paragraph 2) the arteriolar dilation would have to be sufficient to halve the resistance to flow through the arterioles, capillaries and veins in order to restore the total resistance and therefore the flow back to normal, *i.e.*, 0.6 (resistance in the narrowed artery) + 0.64 (resistance in the dilated arterioles) = 1.24 PRU (total resistance). This degree of compensatory arteriolar dilation, however, correspondingly diminishes the amount of dilation which may occur during subsequent periods of increased cardiac work.

Aortic Pressure. Conditions such as aortic insufficiency, arteriovenous fistula, patent ductus arteriosus, communication of the sinus of Valsalva with the right ventricle, and excessive peripheral vasodilation, all tend to produce marked lowering of the aortic pressure during diastole. Since most of the coronary flow occurs in diastole, this may lead to a serious reduction in diastolic coronary flow. The reduction in diastolic flow may be compensated by arteriolar dilation which increases to some extent the proportion of the total flow that occurs during systole. However, as noted in the paragraph above, this reduces the total amount of potential dilation that may be made available during periods of increased cardiac work. The above disturbances also increase the work load on the heart by increasing the cardiac output and thus contribute in a secondary manner to the production of a relative coronary insufficiency.

Hypotension. Decreased mean

* This is approximately the order of magnitude which we have observed

pressure and, as a consequence, lowered diastolic pressure also results from any condition which lowers cardiac output. Included among such conditions are (1) hemorrhage (Master *et al.*, 1950), shock and hyperthermia, all of which may lead to an inadequate volume of blood available to the heart in the central venous reservoir, (2) cardiac tamponade; and (3) acute heart failure from myocardial infarction While the work of the heart is reduced in all these conditions, the head of pressure in the aorta may be reduced so much that the coronary flow is not adequate to supply the basal metabolic requirements plus that of the work being performed, and relative coronary insufficiency may develop. These conditions are discussed more fully on pages 208, 220 and 235.

Hypertension. Hypertension augments the work load on the heart but, fortunately, the elevated aortic pressure also increases the coronary flow directly, thus helping compensate for the increased need for coronary flow. In some hypertensive persons having an arteriosclerotic aorta, however, the rigid aortic wall causes excessive elevation of systolic pressure without much elevation of diastolic pressure. In these subjects the heart has to develop a high pressure to complete ejection; nevertheless, during the major part of the cycle when most of the coronary flow occurs, *i.e.*, during diastole, the aortic pressure is not proportionately increased

Aortic Valvular Stenosis. As a consequence of stenosis of the aortic valve, the work load of the ventricle is increased in order to create the higher intraventricular pressure necessary to eject the blood through the narrowed aortic orifice. In this case, unlike hypertension, the aortic pressure is not elevated and consequently coronary flow is not proportionately increased. The need for increased coronary flow at rest can be met by arteriolar dilation, but here again such dilation limits the subsequent arteriolar dilation that can occur with exercise.

Increased Work Demands, **Elevated Heart Rate.** As indicated in the section on normal coronary flow (page 158), any factor which augments cardiac output increases the need for coronary blood flow. An excessive heart rate also increases the need for coronary flow out of proportion to any associated increase in cardiac output. Of particular importance from the clinical point of view are exercise, eating of meals, chilling of the body and excitement. Extremely strenuous exercise, even in a normal person, can produce a demand greater than the coronary vessels can supply. The various conditions in which the work of the heart is increased are reviewed on page 233 *et seq.* In persons in whom coronary arteriolar dilation is present at rest, this discrepancy between cardiac work and coronary blood supply occurs at much lower levels of cardiac work. Increased heart rate also shortens the time for diastole, relative to the cycle and, thereby, contributes to production of a relative coronary insufficiency.

Myocardial Hypertrophy. As indicated on page 235 myocardial hypertrophy, in response to increased cardiac work, results in enlargement of the myocardial fibers. The number of capillaries is not increased, however, and as a consequence, the effective distance from the center of the myocardial fibers to the capillaries is increased, and the effective supply of oxygen and other nutrients per cubic millim
muscle fiber is reduced. With hyp
of significant magnitude, a relat
nary insufficiency results,
of the factors which limit
trophy.

Active Constriction
It is well known tha
phenomenon, excessive
motor nerve discharg

arterioles of the extremities to become unduly constricted, producing symptoms of inadequate circulation in the feet or hands It has been proposed that a similar phenomenon may occur in the heart, *i e*, that pain impulses from the abdominal or thoracic viscera might reflexly induce a discharge of vasoconstrictor impulses to the coronary arterioles. Such activity might result in relative coronary insufficiency, especially in the presence of narrowing of the arteries. However, clear cut evidence of the existence of such reflexes is lacking; and no evidence has been obtained of the presence of nerve fibers which are vasoconstrictor to the coronary arterioles.

Hypoxia (Anoxia). Even with a normal rate of flow, a relative myocardial insufficiency may be caused by an anemic, an anoxic, or a cytotoxic (sodium cyanide) type of hypoxia (Green and Wegria, 1942) Since myocardial insufficiency is scarcely, if at all, induced by hypercapnia, the immediate participating factor is probably an inadequate oxygen supply *per se*, or the metabolic products resulting from such hypoxia.

PHENOMENA ASSOCIATED WITH CORONARY INSUFFICIENCY

Angina Pectoris. Harrison and Resnik (1950) define angina pectoris as "a clinical syndrome brought about by a temporary discrepancy between oxygen supply and oxygen need in the heart, and characterized by a particular type of pain as well as by the likelihood of sudden death." They emphasize that the term should not be restricted to indicate the pain alone. The pain of angina pectoris is usually felt under the sternum, but occasionally radiates to the neck or either shoulder or arm and occasionally to the epigastrium; it follows promptly the development of a relative coronary insufficiency and disappears equally promptly upon relief of insufficiency. It rarely lasts more than a few minutes.

Genesis of pain. The most probable theory of the production of the pain impulses postulates that when the myocardium suffers from an insufficient or absent blood supply or oxygen delivery, abnormal metabolic products are produced (P factor) which stimulate the pain endings (see Schultz, 1950, for review). This is analogous to the cramping pain which is felt in skeletal muscle when it is exercised during occlusion of the circulation to the muscle (Lewis, 1927, 1931, 1932). Activity or increase in tissue activity appears to be more important than ischemia *per se* in the production of pain, according to Harpuder and Stein (1943a). These authors (1943b) suggest that potassium plays a major role in the genesis of pain. Stretching the coronary vessels or their adjacent structures has been proposed as a mechanism for stimulation of the pain fibers (Katz, 1935, Katz *et al*, 1935 a, b, Martin and Gorham, 1938). It is difficult to see how stretching of the degree induced by these workers could occur in patients. However, it is well known that ischemia greatly sensitizes pain endings (*e.g.*, in patients with peripheral vascular disease) Such sensitization might allow very slight stretching of an ischemic myocardium (Tennant and Wiggers, 1935) to excite the pain endings.

Afferent pathways for the pain impulses. The pain impulses are transmitted by way of the cardiac nerves and the sympathetic ganglia and enter the central nervous system by way of the lower cervical and the upper thoracic roots. Various theories have been proposed to explain the sites of radiation of the coronary pain, none of them is very satisfactory. Radiation almost always extends to areas supplied by somatic fibers which enter the spinal cord at the same level as do the afferent pain fib from the

Myocardial Contractility. *Loss of systolic shortening in the ischemic area.* Complete ischemia rapidly impairs the contractility of the myocardium as described below under coronary occlusion. However, such complete ischemia is not necessary to cause loss of contractility. A relative ischemia, such as can be produced experimentally by rhythmic occlusion and release of a coronary artery at half-second intervals or by coronary arteriolar constriction induced by an intracoronary injection of Pitressin, will cause a sequence of changes of contractility identical with those described below under the heading of Coronary Occlusion (see page 160)

Pulsus alternans. In the presence of relative coronary insufficiency, the refractory period of the affected muscle fibers is nger than normal so that these muscle ers may contract only every other heart-eat. During the intervening beats these muscle fibers are stretched as described above The resulting rhythmic alternation in the strength of the heartbeat and of the arterial pulse is called pulsus alternans (Green, 1936) (see Figure IV-11 and page 184)

Circulation in General. Practically no data are available regarding cardiac output during attacks of angina pectoris. Circulation time and venous pressure are unchanged. About 50 per cent of patients experiencing angina are hypertensives (Altschule, 1949)

Electrocardiographic Changes during Relative Coronary Insufficiency. The electrocardiogram shows nothing between attacks that is characteristic, although, of course, if a patient has hypertrophy or has had a previous coronary occlusion, changes characteristic of these lesions will be noted. However, during an attack of angina, electrocardiographic changes occur which are essentially the same as those seen during the early stages of coronary occlusion.

Tests for Latent Coronary Insufficiency. The two tests most frequently used in patients suspected of having anginal attacks are the exercise (step) test and the hypoxia (anoxia) test. These are designed to bring on a mild relative coronary insufficiency. In the exercise test the patient either makes a series of trips back and forth over a two-step elevation until fatigue or pain occurs or, while lying on his back with his legs extended, flexes his thighs 5 to 20 times, each time touching his toes (Biorck, 1946; Schnitzer, 1949). Electrocardiograms are taken immediately following the exercise Master (1950), summarizing his work and that of his collaborators over the past few years, presents a detailed set of instructions for the "two-step" exercise test Instead of being exercised to the point of fatigue or of onset of pain, the patient is required to make a standard number of ascents, depending on his weight, age and sex. If the RS-T segment is depressed more than 0 5 mm. below the base line, just before the beginning of the QRS complex in any lead, the test is regarded as positive. Master found the chest lead more frequently positive than any of the standard limb leads RS-T depression in precordial leads was consistently associated with RS-T elevation in esophageal leads (Scherlis *et al.*, 1950). Standard limb leads were found preferable to the unipolar limb leads (Chesky *et al.*, 1951).

In the hypoxia test the patient breathes a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes and electrocardiograms are taken at five-minute intervals. If pain develops, the test is stopped immediately and 100 per cent oxygen is given. After the period of hypoxia, the patient breathes 100 per cent oxygen for five minutes and another tracing is then taken (Levy *et al*, 1941 a, b). The hypoxia test

may be more accurate if the degree of hypoxia is controlled with the "ear type" oximeter (Mathers and Levy, 1950, Pennys and Thomas, 1950).

Injection of epinephrine to increase cardiac work has also been employed to induce relative coronary insufficiency The changes in the ECG associated with physiologic tachycardia are of course normal, but any other change in the electrocardiogram, and especially any change in diastolic base line relative to the S-T segment or appearance of abnormal Q, S or T waves, suggests the presence of latent relative coronary insufficiency The tests are potentially dangerous because of the possibility of inducing various cardiac irregularities or even acute coronary insufficiency.

The "meal test" has also been advocated recently as a convenient method for testing patients suspected of having coronary insufficiency (Simonson and McKinlay, 1950, Berman *et al*, 1950). In this test control electrocardiograms are taken, the patient is fed either a 1200-calorie or an 880-calorie meal, and 20 to 30 minutes later, a second electrocardiogram is taken. Abnormal changes in the T waves, *exaggerated or inadequate increase* in heart rate, depression of RS-T segment of 0 05 to 1.0 mm, premature ventricular contractions, and inability to increase the cardiac output adequately were noticed in cardiac patients, particularly in those having angina of effort. Often several of these changes were found in the same patient, while normal controls rarely showed any of these changes and almost never were more than one of them seen in the same subject (Simonson and Keys, 1950).

Relief and Prevention of Attacks by Reducing Heart's Work. Attacks of angina pectoris are usually relieved by anything which decreases the heart's work, these include cessation of exertion, avoidance of large meals and changing from the horizontal to the vertical position, all of which decrease the cardiac output The nitrites which both relieve and prevent attacks are excellent dilators of the coronary arterioles (Boyer and Green, 1941), however, they may be effective because they also tend to cause a peripheral pooling of blood and a decrease in cardiac output. Gradual development of a collateral blood supply to that portion of the myocardium irrigated by a narrow coronary artery may lead to lessening the intensity, and even disappearance, of anginal attacks (Blumgart *et al*, 1950b)

Atherosclerosis. Angina pectoris and coronary occlusion are almost universally associated with the presence in the blood stream of giant lipid and lipo-protein molecules of low density. Both of the latter are also frequently associated with the occurrence of atherosclerosis The prevention and treatment of coronary disease will, therefore, depend on controlling the metabolic and endocrine factors which cause disturbance of cholesterol metabolism (Dock, 1946, Gofman *et al*, 1950, Bloch, 1950) Yater and associates (1948) have reported the incidence of coronary artery disease in 866 soldiers between the ages of 18 and 39 years, 200 of the men were under age 30 The death rates per 100,000 were: age 18-19, 0 1, age 25-29, 1 0, age 30-34, 3 4, age 35-39, 12.7. They examined the survivors of many of these men and also of a control group and found four times as many persons with cardiovascular disease among the survivors of the coronary group as among the survivors of the control group. Obesity was not a factor. All of those examined at autopsy had advanced arteriosclerosis of the coronary arteries.

Cause of Death. Death in these patients often results from non-cardiac causes and

occasionally from heart failure caused by non-coronary cardiac lesions When it follows an anginal attack, death is usually sudden and probably initiated by ventricular fibrillation, since this irregularity has been noted in rare instances in patients who expired while they were having electrocardiograms taken (White, 1944; Munck, 1946; Master, 1947) Pulsus alternans, intraventricular heart block, cardiac "asthma" and congestive heart failure may be preceded by an attack of angina. Occlusion, of course, commonly develops in vessels which have been narrowed to such a degree as to cause angina.

Coronary Occlusion

Sudden interruption of the blood flow in a coronary artery is usually caused by thrombosis or by hemorrhage into an arteriosclerotic plaque With rare exceptions, sudden occlusion is followed by myocardial infarction Occlusion may also occur gradually as a result of progression of the atherosclerosis Occlusion may involve any coronary branch. The incidence of acute and healed infarcts reported by Wang and associates (1948) in 612 cases of occlusion found in autopsies done over a period of 20 years was as follows: left main artery, 6 per cent; anterior descending branch, 47 per cent, left circumflex branch, 13 per cent, descending and circumflex branches of left artery, 6 per cent, right artery 17 per cent, and right and left arteries, 12 per cent. Almost invariably, the greatest functional damage is to the left ventricle. These phenomena are described in detail in Chapter VII

PHENOMENA ASSOCIATED WITH CORONARY OCCLUSION

Pain. The pain associated with coronary occlusion is identical in nature and as far as is known, in mode of production, with that of angina pectoris. However, the pain is frequently more intense, may radiate more widely and always lasts longer, *i e.*, hours to days. Radiation of the pain is more frequently to the left than to the right arm. Pain has been said to be absent in as many as 38 per cent of patients with proven coronary occlusion but, in a series of 56 unselected consecutive cases, White (1948) found that pain had been present in all but two patients. He stated that failure to obtain a history of pain may have been due to the sudden onset of collapse, to concealment by other symptoms or by medication, or to the possibility that it was not adequately sought for. Yater and co-workers (1948) noted pain in 98.4 per cent of 450 soldiers with coronary occlusion, proven at autopsy. About one-half of these had had premonitory symptoms.

Myocardial Contractility. Tennant and Wiggers (1935) attached an optically recording myograph to the fibers of the left ventricle supplied by the descending left coronary artery. Normally these fibers shorten during ventricular ejection and lengthen during ventricular filling. They found that within 30 seconds after they occluded the descending ramus these myocardial fibers ceased shortening during systole. Within one to two minutes the ischemic area behaved like a sheet of rubber, *i e*, with the rise in intraventricular pressure, beginning with isometric contraction, the ischemic area began to stretch. Maximum stretching was reached at the moment of peak of intraventricular pressure The ischemic muscle fibers then shortened during diastole due to their elastic recoil, while the normal fibers were being stretched by the inflowing blood Similar results were obtained by Prinzmetal and associates (1949), using the technic of slow-motion color pictures This "non-contractile" portion may contract in response to electrically induced premature systoles and shows unimpaired conduction. Tennant (1935) was able to produce sys-

tolic elongation of a localized area of myocardial fibers by intracoronary arterial injection of potassium chloride, sodium cyanide and sodium lactate in the presence of normal oxygenation. He postulated that excess lactate might be a factor in preventing contraction under anoxic conditions

The loss of contractility has two effects One effect is the loss of the contribution to the force of ejection which normally would have been provided by the ischemic muscle, thus throwing the entire load on those myocardial fibers which still contract. The second effect results from bulging of the ischemic muscle during systole This bulging serves to accept some of the force of ejection of the remaining active muscle which must do an extra amount of work to stretch the ischemic muscle over and above that normally necessary to eject the blood from the ventricle The bulging area may fail to be converted to a firm scar and may remain as a ventricular aneurysm This phenomena was noticed by Berman and McGuire (1950) in 9.4 per cent of 192 consecutive cases of myocardial infarctions studied at autopsy. The aneurysmal wall was, however, apparently firm enough so that rupture had not occurred in any of these subjects

Cardiac Rupture. Usually the necrotic muscle fibers, which have lost their blood supply because of occlusion of a coronary artery, are replaced by firm scar tissue Before scarring can occur, however, the pressure in the left ventricle during systole may force the blood to burrow through the necrotic myocardial fibers and eventually to rupture the wall. Perforation of the septum will allow blood to be forced into the right ventricle. Perforation of the wall externally will allow blood to be forced into the pericardial sac and will lead rapidly to death through cardiac tamponade

Cardiac rupture has been reported to occur as early as a few hours and as late as three weeks after coronary occlusion. Rupture has been reported to occur in as few as 5 per cent and as many as 73 per per cent of cases of acute myocardial infarction (White, 1944, Zinn and Cosby, 1950, Gans, 1951) The influence of activity on the development of cardiac rupture is brought out by two comparative studies Rupture was found in 9 5 per cent of 105 hearts with acute infarction at autopsy in hospitalized patients (Friedman and White, 1944), in contrast, rupture was found in 73 per cent of hearts of 22 patients who died in a mental institution from recent infarcts (Jetter and White, 1944). In neither study were any instances of rupture encountered among 165 and 25 hearts, respectively, with old healed infarcts The anterior wall of the heart appears to be most susceptible In a series of 23 ruptured hearts observed at autopsy and reported by Wang and associates (1948), rupture occurred in the anterior wall of the left ventricle in 21, in the anterior wall of the right ventricle in 1, and in the septum in 1, in the same series, anterior infarctions were only about twice as common as posterior.

Collateral Circulation, Myocardial Necrosis. Frequently, at autopsy, one or more coronary arteries are found to be completely occluded, yet the myocardium customarily supplied by these vessels appears normal. Evidently either a collateral supply to this muscle had developed or the patient had died before myocardial necrosis had had time to develop. The frequency with which the latter may occur is indicated in the study by Yater and co-workers (1949) who noted absence of myocardial infarction in 336 of 450 soldiers that died of acute coronary disease, and lack of complete occlusion of a coronary artery in only 38 of these young patients. As indicated in the section on Normal Coronary Flow (page 160), a considerable period of tim

must elapse before collateral circulation can become adequate to keep the muscle viable Therefore, if necrosis is to be prevented, occlusion must take place gradually rather than suddenly, allowing time, and providing the stimulus, for a collateral circulation to develop.

Circulatory Dynamics. A large infarction may be followed by acute left heart failure (see section on Heart Failure, page 235) On the other hand, phenomena characteristics of a shock-like state may be seen during the first few hours or days The shock symptoms include low mean-arterial pressure, narrow pulse pressure, tachycardia, pallor, sweating, low venous pressure and diminished size of the superficial veins (venous constriction ?). The cause of the shock-like state is not known. It may be reflexly initiated by the pain impulses In the presence of a shock-like state some physicians withhold fluids for fear of overloading the heart The consensus would seem to indicate, however, that fluids may be given as long as symptoms of acute or chronic congestive heart failure are absent (Schwartz, 1947). Furthermore, Agress and associates (1950) found that the plasma volume and blood volume were reduced soon after the onset of myocardial infarction. However, Epstein and Relman (1949) concluded, after comparing the results in 30 patients who were transfused and 20 patients who were not, that "although transfusions seemed to be of benefit in a few cases, there was no significant difference between the two groups in mortality and recovery from shock. Transfusion did not seem to increase the incidenec of pulmonary edema or the severity of congestive failure."

Cardiac Irregularities. Premature beats, tachycardias and especially ventricular fibrillation which frequently follow coronary occlusion are probably generated in the hyperirritable junctional area of partially ischemic muscle tissue between the infarcted and the surrounding normal myocardium (Wiggers, 1945). Altschule (1949) believes that partial heart block and atrial flutter and fibrillation which may occur after infarction are due to reflex initiation of excessive vagal discharges (see section on Cardiac Irregularities, page 175). Harris (1950) noted that the maximum rate of ectopic impulse initiation occurs at about the time that the earliest microscopic signs of necrosis have been found. He suggests that the initiation of ectopic impulses probably occurs at the boundary between ischemic and non-ischemic tissue, and that the "hyperirritability" of this area is "enhanced" by cat-electrotonus from the injury potential and possibly also by sympathoadrenal substances, histamine and other substances formed or liberated during necrosis.

Miscellaneous Associated Phenomena. Mild fever (100 to 101° F.), leukocytosis, and an increased rate of blood sedimentation follow myocardial infarction These are probably initiated by products absorbed from the necrotic myocardium. Creatinuria, nitrogen retention, jaundice, gastrointestinal disturbances and the shoulder-hand syndrome are occasionally encountered following occlusion. A mild pericarditis may develop over the surface of the infarct and give rise to a friction rub. Not infrequently, thrombi develop on the endocardium in the area of the infarct These may become dislodged, giving rise to pulmonary emboli when they arise in the right atrium or ventricle and to systemic emboli when they arise in the left ventricle. Thromboembolic phenomena were noted by Zinn and Cosby (1950) in 21 per cent of 679 autopsy-proven cases of myocardial infarction. These complications are more fully discussed in Chapters VII and XIII.

Electrocardiographic Changes Following Coronary Occlusion. Electrocardiographic changes following coronary occlu-

sion are discussed in Chapter XIII on Clinicopathologic Correlations See also standard reference books on electrocardiography (Graybiel and White, 1946, Katz, 1946, Goldberger, 1947; Burch and Winsor, 1949; Hecht, 1950; Wolff, 1950)

Physiologic Basis for Therapy. The principles involved in the therapy of coronary occlusion are clear-cut and based upon a knowledge of the disturbances in physiology. They include relieving the initial shock-like state, reducing the cardiac work to a minimum until a firm scar has formed, use of drugs to reduce the irritability of the myocardium (*i e*, to increase the refractory period relatively more than the slowing of conduction), use of anticoagulants to minimize formation of thrombi and production of emboli, and artificial creation by surgical means of additional collateral blood supply to the heart.

For comparison with patients treated with anticoagulants, statistical data on the incidence of death and of thromboembolism during the past 20 years in patients not receiving anticoagulant therapy have been reported by Doscher and Poindexter (1950) They noted in their own series of 414 patients with myocardial infarction that 15.5 per cent died and 6.5 per cent had one or more thromboembolic attacks. They also reviewed 4108 cases reported in the literature The death rate for the two groups when pooled was 23 5 per cent and the incidence of thromboembolic phenomena was 10 8 per cent.

According to Wright and associates (1948), in a series of 368 patients with coronary thrombosis who did not receive anticoagulants the over-all death rate was 24 per cent, and thromboembolic complications occurred in 26 per cent. On the other hand, among 432 patients treated with anticoagulants, the death rate was 14 9 per cent and thromboembolic complications were recorded in 12 per cent Nichol and Borg (1950), who administered Dicumarol to 78 patients over many months, reported that its use decreased the immediate death rate and the incidence of thromboembolism and seemed to decrease the number of recurrent attacks, but was attended by major hemorrhagic episodes in 13 patients (with death in 2)

Master and associates (1939) concluded from an analysis of the frequency distribution of attacks during the various hours of the day that coronary occlusion occurs irrespective of the state of physical activity However, when one observes the onset of an attack during excitement or strenuous exertion, one is inclined to believe that there may be some causal relationship between activity and the onset of occlusion, especially if the occlusion be found to have been caused by an embolus or an intramural hemorrhage.

4. EXTRACARDIAC DISTURBANCES WHICH AFFECT THE HEART

Disturbances Which Interfere with Cardiac Filling

Angulation and Rotation of the Heart. Angulation and rotation of the heart occur during surgery on the heart or mediastinal structures, as a consequence of excessive pneumothorax (either accidental or intentional, as in the treatment of pulmonary tuberculosis), and as a result of infections in the region of the heart which produce adhesions between the heart and chest wall. Such dislocations cause failure of filling or of emptying of the cardiac chambers by compressing the various vessels where they penetrate the pericardium. As a result of the sudden displacement of the heart, systemic arterial pressure suddenly drops. In a patient with adhesions between the heart and anterior chest wall fainting was produced by hyperexpansion of the chest; the fainting could be relieved by bending forward. Because of the im-

pairment in output, prolonged periods of displacement of the heart should be avoided during thoracic surgery (Beck, 1944).

Traction on the Heart. Traction has been given as the cause of hypertrophy in hearts that were bound by adhesions to various thoracic structures. However, Beck (1944) found that traction in the longitudinal axis had no effect on cardiac output or systemic arterial pressure, and that traction in other directions served mainly to reduce cardiac output by narrowing the lumen of the vessels that enter or leave the heart. He found many instances of hypertrophy of the heart associated with intrinsic cardiac lesions, such as vascular anomalies and valvular defects. However, even in the presence of pericardial adhesions, hypertrophy was absent when the remainder of the heart was normal.

Acute Cardiac Compression. Cardiac Tamponade (Pericardial Effusion). *Dynamics* Elevation of pericardial pressure by accumulation of air, blood, exudate or transudate within the pericardial sac tends to collapse the veins where they enter the pericardium and also to collapse the heart chambers The compression prevents proper ventricular filling and reduces cardiac output. The reduced output causes the systemic and pulmonary venous pressures to rise. The rise in systemic venous pressure is related to the available blood volume and to the degree of veno-constriction. Within limits, the elevation of venous pressures tends to compensate for the rising pericardial pressures and maintains cardiac filling and cardiac output. However, if the pericardial accumulation becomes excessive, the entering veins and the cardiac chambers tend to collapse and the cardiac output becomes markedly reduced. The critical pericardial pressure at which cardiac output fails is around 10 to 18 cm. of saline (Adcock *et al.*, 1940, Beck, 1944; Fletcher, 1945, Warren *et al.*, 1946; Lyons and Burwell, 1946; Nerlich, 1951).

Distinction of massive pericardial effusions from large dilated hearts is possible on the basis of the arm-to-tongue circulation time (Bellett *et al.*, 1951). In the former, the time is less than normal or at most only slightly prolonged (8 to 22 seconds; average, 16 seconds in 17 patients), whereas with dilated hearts the circulation time would be expected to be markedly prolonged.

Pulsus paradoxus. Pericardial effusions of a magnitude less than that which causes failure of cardiac output frequently cause an accentuated decrease of mean arterial pressure and of the arterial pulsations in late inspiration or early expiration, and an increase in arterial pressure and pulsations in late expiration or early inspiration These changes in pulsations, called the paradoxic pulse, appear to be caused by rhythmic intrathoracic pressure changes which have their normal effect on the central systemic veins and on the quantity of blood in the lungs but are unable simultaneously to affect the cardiac chambers. There is thus an accentuated effect of respiration on cardiac filling and output (Gauchat and Katz, 1924; Katz and Gauchat, 1924; Beck, 1944).

Clinical signs. The main findings in acute cardiac compression are falling arterial pressure, rising venous pressure and a small quiet heart. When caused by a perforating wound of the heart, the condition constitutes an emergency requiring immediate surgical intervention and closure of the perforation since the heart continues to pump blood into the pericardial sac through the perforation as long as the heart is able to contract.

Pneumopericardium In experimental animals exposure of the heart or even of the pericardium to atmospheric pressure raises the absolute pressure on the outside of the cardiac chambers (reduces the

negative pressure to zero). This pressure change causes alterations in cardiac dynamics suggestive of cardiac compression With permanent exposure to atmospheric pressure there is a sustained decrease in cardiac output of 20 to 25 per cent, a sustained increase in arteriovenous difference in blood oxygen content and in systemic venous pressure, but only a momentary decline in systemic arterial pressure (Beck and Cox, 1930).

Chronic Cardiac Compression. Constrictive Pericardium. This condition is frequently designated as constrictive pericarditis, adhesive pericarditis, mediastinal pericarditis, Pick's disease or Concato's disease. Since, however, acute inflammation plays no part in the symptomatology, the suffix "-itis" should probably be abandoned. The disturbance is produced by the contraction of the scar tissue and usually occurs long after the acute inflammatory process has subsided The term "adhesive pericarditis" should also be abandoned since all the manifestations are caused by compression of the heart This compression may be caused by chronic accumulation of fluid (Barker and Johnston, 1950), but is usually due to compression by scar tissue (Beck, 1944)

Cardiovascular effects of chronic cardiac compression The effects produced by chronic cardiac compression are similar to those of acute cardiac compression The compression causes lowering of cardiac output because of inability of the ventricles to fill completely and of resulting depression of systemic arterial pressure and elevation of systemic venous pressure. Because of the more prolonged nature of the disease, compensatory changes characteristic of those seen in chronic congestive heart failure develop (see section on Heart Failure, page 236). These include increase of blood volume (which may be as much as 1 liter above normal), and retention of salt and water with resulting enlargement of the liver, pleural effusion, ascites and dependent edema (Fishman *et al.*, 1950). Associated symptoms and signs are cyanosis, breathlessness, distended veins and pulsus paradoxus

Constrictive pericarditis over the left ventricle has been described by White and associates (1948) Their patients showed accentuated pulmonic second sounds, right ventricular enlargement, right axis deviation in the electrocardiogram and marked elevation of the pulmonary capillary pressure Of 3 patients, 1 died and 2 were benefited by surgery.

Cardiac work in presence of chronic cardiac compression. Contrary to conditions leading to chronic heart failure, the work of the heart is reduced in cardiac compression and the heart atrophies Fluoroscopic examination reveals decreased cardiac action. Surgical excision of the constricting pericardium often cures this type of cardiac disturbance (Beck, 1944)

Chronic pericardial effusion In 2 of 3 patients with pericarditis with chronic effusion, Barker and Johnston (1950) noticed a prominent third heart sound in early diastole which was heard best at the apex and which superficially resembled the murmur of mitral stenosis. This murmur had developed after the onset of atrial fibrillation and was believed to have been caused in each case by the presence of a large organized thrombus in the right atrium All three patients developed atrial fibrillation In two of the subjects electrocardiograms taken prior to fibrillation had shown broad notched atrial waves, and at autopsy the atria were hypertrophied while the ventricles were atrophied (Barker and Johnston, 1950).

Ball-Valve Thrombus. A rather rare condition which may lead to impairment of cardiac filling is a free floating or a pedunculated ball-valve thrombus. Such thrombi have been noted most frequent

in the left atrium in the presence of mitral stenosis (White, 1944), and in the right atrium in the presence of chronic cardiac compression combined with atrial fibrillation (Barker and Johnston, 1950). Thrombi within the four cardiac chambers are quite common but, fortunately for the patient, they rarely develop the ball-valve form.

Ball-valve thrombi in the atria may offer a constant impediment to ventricular filling, thus resembling mitral or tricuspid stenosis, or they may occlude the opening only periodically Periodic occlusion causes sudden attacks of syncope, decreased cardiac output and feebleness of the pulse (White, 1944) When present in the right atrium, the patient may show dusky cyanosis of the face and neck, engorgement of veins of the face and neck and of the liver with a systolic pulsation in these structures, marked dyspnea of the oxygen-hunger type without signs of respiratory obstruction, enlargement of the right atrium, evidence of old rheumatic heart disease, atrial fibrillation, a murmur suggesting tricuspid stenosis, and rapid fluctuations in severity of symptoms over short periods of time. The diagnosis probably could be aided by registration of pressures in the heart chambers, and by x-ray visualization of the cardiac chambers with Diodrast (Wright *et al*, 1944).

Asthma, Pneumothorax and Pleural Effusion. These often cause a mild elevation of the central systemic venous pressure, measured relative to atmospheric pressure The elevation is related to the increase in absolute pressure in the thorax (intrathoracic pressure is less negative) which impairs to some extent the return of blood to the heart. Measurements of cardiac output are scarce but those available suggest that little deviation from normal occurs at rest (Altschule and Zamcheck, 1944, Altschule, 1949).

Explosive Decompression. In the pressurized cabin of an airplane the air pressure within the cockpit or cabin is maintained at the equivalent of no more than 10,000 feet altitude. An anti-aircraft shell can make a large hole in the wall of such a cabin. If the hole should develop when the airplane was flying at 40,000 feet, the pressure in the cabin would drop suddenly from 522 to 140 mm. Hg. This drop may occur in as little as 0.2 to 0.005 second, and the phenomenon is, therefore, designated explosive decompression.

Normally man and animals readily tolerate explosive decompression but, if the degree or the rapidity of change is great enough, a momentary decline in arterial pressure may occur. This decline in arterial pressure is principally caused by maintenance of the intrathoracic pressure for the time being at around 522 mm. Hg while the rest of the body is exposed to a pressure of 140 mm. Hg. This produces the effect of mild tamponade equivalent to that seen in emphysema or pneumopericardium (see above). The effect is aggravated by increasing the altitude of the plane at the time of decompression and by shortening the time of decompression (Gagge and Shaw, 1950). Any resistance to expiration, such as spasm of the glottis, aggravates the effect since such resistance delays the drop in intrathoracic pressure (Whitehorn *et al*, 1946; Benke, 1950).

If the elevation of the plane at the moment of explosive decompression is above 75,000 feet, more severe symptoms may occur, since at this altitude body fluids tend to boil and extreme distention of all bodily tissues occurs. In experimental studies on monkeys, exposed to decompression equivalent to 75,000 feet in 0.2 second, cessation of respiration, bradycardia, reduction of systemic systolic and diastolic arterial pressures and disruption of the normal electrocardiogram were observed. When breathing of 100 per cent oxygen

was begun immediately and the monkeys were recompressed at the free fall rate (in approximately five minutes), all began to recover and arterial pressures, respirations and electrocardiograms were normal by the time sea-level pressure was reached (Gelfan, 1950, Gelfan *et al*, 1950).

Disturbances Affecting Primarily the Pulmonary Circulation

ACUTE COR PULMONALE

Pulmonary Embolism. Pulmonary emboli usually arise from thrombi which have broken loose from the deep veins of the legs (Spitzer *et al.*, 1949). They have been found also with congestive failure associated with mitral stenosis and hypertensive heart disease, and after myocardial infarction. The emboli usually lodge in the lower lobes, especially of the right lung Infarction of the lung frequently occurs in association with congestive failure Pulmonary emboli may also be the result of accidental introduction of oil or air into a vein.

Symptoms and signs of pulmonary emboli. Symptoms and signs of pulmonary embolism include oppression or pain in the chest, pleuritic pain and often hyperesthesia to percussion (McMillan, 1950), cough and occasionally blood-tinged sputum, air hunger and, when the emboli are large enough, signs of right ventricular failure or of a shock-like state. Friction rub, pleural effusion, signs of consolidation, cyanosis, jaundice, fever and hyperpnea may also be present.

Circulatory dynamics during pulmonary embolization. Serious obstruction to the blood flow in the pulmonary arteries probably occurs only when emboli occlude 50 per cent or more of the pulmonary arterial system (Fineberg and Wiggers, 1936), *i e.*, when large or multiple emboli lodge in each pulmonary artery or a rider embolus lodges in the bifurcation of the pulmonary trunk (White, 1944) The impediment to flow causes retention of blood in the right ventricle, leading to a rise of right atrial and right ventricular initial pressures, and to an increased force of right ventricular ejection with elevation of intraventricular peak systolic pressure and of the pressure in the proximal segment of the pulmonary trunk The mean and pulse pressures decline in the segments of the pulmonary artery distal to the emboli (Megibow *et al.*, 1942, Katz, 1945; Levy and Berne, 1949). If right ventricular output fails to be maintained, left ventricular output falls and this causes syncope or a shock-like state with *peripheral vasoconstriction* Severe tachycardia (Renner, 1949) or atrial flutter or fibrillation may also develop Physical examination may reveal a systolic murmur which is produced by a functional tricuspid insufficiency, and a systolic murmur, an accentuated second sound and a to-and-fro rub in the pulmonic area which may be produced by the dilation of the right ventricle and pulmonary trunk.

Electrocardiographic changes resulting from pulmonary embolism The electrocardiogram may show temporary, marked right axis deviation with a deep S and an *elevated diastolic base line in lead I and a* deep Q, a depression of the diastolic base line and inversion of the T in lead III. When electrocardiographic evidence of cardiac damage, particularly left axis deviation, is present prior to the occurrence of the pulmonary embolism, the subsequent electrocardiographic changes may be even more marked (Dack *et al*, 1949). These electrocardiographic changes could be produced by relative ischemia of the right ventricle with rotation of the heart so as to place the anterior portion of the septum more to the left.

Gross or histologic evidence of myocardial necrosis or infarction, usually involving the left ventricle, was found in 10

of their 41 cases by Dack and associates (1949) They felt that the damage was caused by diminished coronary flow and myocardial anoxia which resulted from the systemic-shock-like state, the right ventricular dilation, the anoxia and possibly from reflex vasoconstriction. The last seems unlikely, however, since Malinow, Katz and Kondo (1946) found that vagotomy had no effect on the electrocardiographic changes after experimental pulmonary embolism and concluded that "no ground exists for the assumption of a vagal pulmonocoronary constriction reflex in pulmonary embolism" (see also Eckardt, 1938).

Pulmonary air embolism Durant and associates (1947) studied the phenomena of pulmonary air embolism in dogs. They found that the amount of air needed to cause death varied widely depending upon the speed of injection, the position of the dog and the ability of the animal to excrete the air lodged in the pulmonary capillaries by developing tachypnea. As little as 25 to 50 ml. of air caused death of animals in which the thorax was opened and in which tachypnea could not occur. Other intact, but anesthetized, dogs survived several successive injections, each of 100 ml One animal survived injection of a total of 1000 ml. of air These workers noted that, with the dog supine, air accumulated in the outflow tract of the right ventricle and produced an air lock Shifting the position so that the animal lay on its left side caused frequent survival, even when the right ventricle and atrium were greatly dilated and right ventricular beats were very weak prior to changing the position of the animal.

Electrocardiographic changes resulting from air embolism. Electrocardiograms recorded from intact dogs during the formation of air emboli showed elevation of the diastolic base line in leads II and III with lowered T waves but no change in the diastolic base line in lead I. Various degrees of A-V block or nodal rhythm were frequent (Durant *et al.*, 1947). These changes are suggestive of ischemia involving the mid-portion of the anterior surface of the heart. Interestingly enough in experiments on open-chested animals these authors found an apparently ischemic area on the anterior surface of the heart which was supplied by the distal branches of the anterior descending branch of the left coronary artery. Electrocardiograms taken with an electrode on this ischemic area yielded monophasic curves with the diastolic base line deviated in a direction which was characteristic of myocardial injury under this electrode These authors felt that the right ventricular ischemia was caused by the excessive pressure within the right ventricle which interfered with adequate coronary blood flow, but they were unable to explain why the ischemia was grossly evident in only one part of the right ventricular muscle.

Ligation of the Pulmonary Artery. In pneumonectomy it is necessary to ligate the corresponding pulmonary artery In a series of 12 patients subjected to pneumonectomy no significant changes were noted in electrocardiogram, ballistocardiogram or arterial blood pressure in comparison with normal subjects (Cournand and Berry, 1942). In a more recent series of patients undergoing pneumonectomy, cardiac catheterization was carried out before, during and after operation The operation consistently caused an immediate elevation of the pulmonary arterial pressure amounting, on the average, to 50 per cent of the basal level. However, the pressure usually returned to basal levels by the time the operation was completed (Zimmerman *et al.*, 1949).

In one patient studied two years after ligation of the left pulmonary artery, the cardiac output was increased but the pressures were normal in the right ventricle and pulmonary artery. Considerable

collateral anastomoses had probably developed between the bronchial arteries and the capillary bed of the left lung (Roh *et al.*, 1949).

Elevation of Pulmonary Capillary Pressure. Elevation of the pulmonary capillary pressure usually results from failure of the left ventricle or from mitral stenosis The elevation may be brought on acutely by any factor which suddenly increases the systemic venous return, such as infusions, exercise or dreams. Pulmonary capillary pressure may also be increased by sudden elevation of the systemic arterial pressure by large injections of epinephrine or the physiologic output of epinephrine that accompanies central nervous system ischemia. These phenomena are described in the sections on Elevation of Arterial Pressure (see pages 214 and 216) and on Heart Failure (see page 232)

A rise of 50 to 260 per cent in mean pulmonary arterial pressure has been recorded in normal subjects receiving one liter of physiologic saline intravenously within 10 minutes "Pulmonary capillary pressure" responded by a similar increase Heart rate remained constant Neither cardiac output nor the volume of blood in the lungs, measured by the dye method, could be correlated with the rise in pulmonary arterial pressure. On the basis of these findings, Warren and associates (1950) concluded that the rise in pulmonary artery pressure is a "back pressure" effect. They felt that even more striking effects might occur in patients with cardiac disease and that these changes might be an important factor in the genesis of pulmonary edema

CHRONIC COR PULMONALE

Chronic Pulmonary Disease. Pulmonary Fibrosis. Emphysema. Ayerza's Syndrome. Insofar as the heart is concerned, most chronic pulmonary diseases may be grouped together They are all associated with cyanosis due to the increased degree of arterial oxygen unsaturation produced by ineffective alveolar ventilation (Comroe and Fowler, 1950) and the associated polycythemia. Pulmonary arterial systolic and diastolic pressures, and right ventricular systolic and right atrial pressures are usually elevated at rest (Borden *et al*, 1950) and increase excessively with slight exercise The blood volume is increased but cardiac output, arteriovenous oxygen difference and systemic arterial pressure are usually normal in the absence of heart failure (Bloomfield *et al*, 1946, Taquini *et al*, 1947, Riley *et al*, 1948, Hickam and Cargill, 1948).

The elevated pulmonary artery pressure at rest is caused by constriction and possibly also by some obstruction of the small arteries of the lungs (Leopold, 1950, Wolman, 1950) The constriction may be related to the anoxia since short periods of anoxia cause acute elevation of the pulmonary arterial pressure (Motley *et al*, 1947). Heart failure associated with cor pulmonale was found to be accompanied by a resting cardiac output above normal and with excessively elevated mean pulmonary arterial and right ventricular systolic and diastolic pressures During the initial period of treatment with Digoxin, the cardiac output and pulmonary arterial pressures increased slightly and the diastolic pressures fell After prolonged treatment, dyspnea and cyanosis disappeared, and the heart size, pulmonary arterial pressure, right ventricular initial pressure and cardiac output had almost returned to normal, and the arterial oxygen saturation had risen These findings also suggest that this kind of heart failure is the high-output type and may be associated with constriction of small pulmonary arteries which is reversible (Cournand, 1950, Ferrer *et al.*, 1950). Relief from the symptoms of cor pulmonale has also resulted from reduction of thyroid activity with Thiouracil

although the arterial oxygen saturation may then remain below normal (Sharpey-Schafer, 1946).

Disturbances Affecting Primarily the Systemic Circulation

CONDITIONS CAUSING INCREASED RESISTANCE TO BLOOD FLOW IN THE SYSTEMIC CIRCUIT

Hypertension. *Increased peripheral resistance in hypertension.* It is generally agreed that in systemic arterial hypertension cardiac output is normal but total peripheral resistance is increased A large number of causes have been proposed for the increase in peripheral resistance in human hypertension. It is beyond the scope of this chapter to discuss them The most common types of hypertension are probably basically caused by increased tone of the vasomotor system, which is attributable to a renal pressor effect or to an altered anterior pituitary-adrenal cortex relationship The reader may refer to Fishberg (1939), Goldring and Chasis (1944), Braun-Menendez and associates (1946), Goldblatt (1947), Shorr (1948), Page (1949), Page and Corcoran (1949), Wiggers (1949), Wilkins and associates (1949), Gressel and associates (1949), and Wakerlin (1949) for detailed information.

Aortic pressure in hypertension. In order to overcome the increased resistance to flow of blood through the systemic arterioles the heart has to create a higher pressure in the aorta and systemic arteries. The higher arterial pressure leads to a greater average distention of the aorta under which condition it is less distensible than normal (Hallock and Benson, 1937). As a consequence of the greater rigidity of the aorta, the pulse pressure is wider than normal even though the stroke volume output of the heart is within normal limits (Green, 1950)

Effects of hypertension on the heart. The elevation of arterial pressure causes increased left ventricular work and leads to left ventricular dilation and hypertrophy and to an accentuated aortic second sound. The left ventricular enlargement is demonstrable fluoroscopically and by electrocardiograms (Bechgaard, 1949). Right ventricular pressure usually remains normal in the absence of complications but was found to have risen in 10 of 13 patients with the malignant phase of hypertension (Lenegre and Maurice, 1947). Coronary blood flow increases with the rising arterial pressure (see Disturbances of Coronary Circulation, page 158) Elevation of the systemic arterial pressure predisposes to atherosclerosis and thereby increases the likelihood of thrombotic complications in vessels such as the arteries of the brain, heart, kidneys and lower extremities.

Treatment of hypertension. Symptoms associated with hypertension, such as headache and dizziness, are usually unrelated to the heart unless heart failure is present. Variable degrees of reduction of arterial pressure and cardiac work and relief of symptoms in essential hypertension are reported after extensive sympathectomy (Fishberg, 1948, Peinck, 1949, Smithwick, 1949, Grimson *et al*, 1949, Hammarstrom and Bechgaard, 1950) and after prolonged use of low sodium diets (Schroeder *et al.*, 1949), of the rice diet (Kempner, 1945, 1946, 1948) and of certain hypotensive drugs (Meilman and Krayer, 1950; Coe and Best, 1950; Nickerson, 1950). Cortisone and ACTH alone were found to have minimal effects on the cardiovascular system of patients with essential hypertension, but restoration of normal salt intake during ACTH (adrenocorticotropic hormone) administration caused a striking rise in stroke volume output and in the appearance of a "strain" pattern in the electrocardiogram (Perera *et al.*, 1950, Ransohoff *et al.*, 1950).

Polycythemia. Increase in the concentration of red cells in the blood, in the hematocrit reading, in the oxygen-carrying power of the blood, and in the total circulating blood volume occurs as a physiologic response to many kinds of anoxia (secondary polycythemia). Increased red cell counts and hematocrit readings are also seen in polycythemia vera in which no cause for the increased quantity of red cells can be demonstrated

In both kinds of polycythemia the blood becomes much more viscid, the resistance to flow through the arterioles and capillaries being greatly increased (Whittaker and Winton, 1933, Green *et al*, 1943, Green, 1950). The increased viscosity is to some extent compensated by peripheral arteriolar vasodilation. The latter causes, in turn, capillary dilation and the associated reddish blush of the skin (Jeghers, 1950). Despite the peripheral vasodilation, moderate systemic hypertension, increased cardiac work and moderate cardiac hypertrophy may be seen (Brooks, 1936) Vascular thromboses are common (White, 1944). Radio-sodium — Na^{24} (Low-Beer, 1950) and radio-phosphorus — P^{32} (Solomon, 1950) have been used to reduce the red cell concentration and, thereby, the blood viscosity

Effects of Excessive Quantities of Sympathetic Chemical Mediators. *Causes of excessive blood concentration of sympathomimetic substances.* Epinephrine and epinephrine-like substances are released from the adrenal gland and at the terminals of the postganglionic sympathetic fibers in the tissues during activity of the sympathetic nervous system. These substances are not completely destroyed in the tissues. As a consequence they diffuse into the blood and are thus capable of exerting sympathomimetic effects in other parts of the body. The quantity of these substances reflects the activity of the sympathetic nervous system Excessive quantities of sympathetic chemical mediators may be present in the body as a result of accidental injection of abnormally large doses of epinephrine (McGinty and Baer, 1947) or as a physiologic response to conditions of extreme stress such as the development of shock (Green *et al.*, 1950), severe anoxia (Van Loo *et al.*, 1948) in the presence of a pheochromocytoma (Goldenberg and Aranow, 1950), or during severe ischemia of the central nervous system (Guyton, 1948, Green *et al.*, 1950), and as a result of loss of the moderator impulses from the pressor receptors in the carotid sinuses and aortic arch.

Effects of injection of excessive quantities of epinephrine in man and experimental animals Accidental injections of large amounts of epinephrine into patients may lead to precordial distress, increase of sedimentation rate, elevation of body temperature, and electrocardiographic changes suggestive of relative coronary insufficiency The last is indicated by a slight depression of the diastolic base line in leads II and III, and inversion of the T in lead I and large upright T waves in leads II and III. Epinephrine may occasionally induce ventricular premature beats, tachycardia or fibrillation, these are particularly likely to occur in the presence of chloroform or cyclopropane anesthesia.

In dogs and guinea pigs excessive quantities of these chemical mediators, whether injected or produced in response to stress, cause a marked rise in systemic arterial pressure, bradycardia, elevation of pulmonary arterial pressure, cardiac dilation and pulmonary edema (MacKay and Pecka, 1949). The latter probably results from the high pulmonary capillary pressure caused by a rise in left atrial pressure. In this condition bilateral vagal stimulation causes a fall in arterial pressure and prevents the pulmonary congestion and edema (Paine *et al*, 1949).

In rats, dogs and cats it has been shown that large doses of epinephrine appeared to cause death because of respiratory paralysis which could be prevented by artificial respiration (Nickerson *et al*, 1950). The inhibition of respiration was a direct effect of the epinephrine on the medullary centers, for it was not prevented by cutting the afferent nerve fibers which arise in the presso-receptors, this was accomplished by combined vagotomy and carotid artery ligation or section of the glossopharyngeal nerves (Hoff *et al.*, 1950).

Experimental neurogenic hypertension. Moderate increase of sympathetic tone occurs in experimental neurogenic hypertension induced by sectioning the afferent moderator nerves from the carotid sinus and aortic arch. In experiments of this type it was noted that cardiac output rose, the arteriovenous oxygen differences and the coefficient of oxygen utilization both decreased, heart rate increased, but stroke volume and right atrial pressure remained unchanged. Blood flow in the kidney fell while that in the forepaw rose (Bing *et al*, 1945).

EXCESSIVE CARDIAC OUTPUT CAUSED BY ABNORMALLY INCREASED VENOUS RETURN

Venous return to the heart may be elevated above normal by too-rapid intravenous infusion of saline, and especially of plasma or whole blood Venous return is also increased by conditions which induce peripheral arteriolar but not venous vasodilation.

Increased venous return leads successively to augmented right atrial pressure (Warren *et al.*, 1948), increased right ventricular output, elevated pulmonary blood flow, and increased left ventricular output (+ 2 to + 122 per cent). Pulmonary flow of greater than 7 l./min./M² leads to dilation and increased pulsation of the pulmonary trunk, flows less than this rarely do so, unless accompanied by increased pulmonary artery pressure. Heart rate and systemic arterial pressure change but little (Fletcher *et al.*, 1945) and peripheral resistance increases (Holt and Knoefel, 1944).

Increased venous return caused by the above conditions is usually temporary and with normal hearts causes no difficulty. A sudden increase in venous return can, however, throw a damaged heart into acute heart failure, usually of the left ventricular type (see section on Heart Failure, page 238) Associated with the failure will be increased pulmonary blood volume and elevated systemic and pulmonary arterial and systemic central and peripheral venous pressures and increased cardiac and respiratory rates (Drinker *et al*, 1926). The difference between peripheral and central systemic venous pressure will be reduced (Huckabee *et al.*, 1950). In the absence of failure, infusions usually lead to increased renal blood flow and glomerular filtration and efferent renal arteriolar dilation as represented by a reduced filtration fraction (Wilson and Harrison, 1950).

INCREASED CARDIAC OUTPUT CAUSED BY EXCESSIVE DECREASE IN PERIPHERAL RESISTANCE

Peripheral Vasodilation Associated with Increased Metabolic Rate. The metabolic rate of the body, as indicated by measures of oxygen consumption, is increased physiologically in exercise, after meals, during pregnancy, with overweight, with hyperthyroidism (see page 218) and during fever.

Pregnancy. Cardiac output begins to increase early during pregnancy and reaches a peak of around 20 to 25 per cent above normal at about the thirty-second week; it returns to normal near term. A second

marked increase in cardiac output occurs during the first and second days postpartum. In the presence of a damaged heart, heart failure is most likely to occur about the thirty-second week or the immediate postpartum period when cardiac output is highest. Occurrence of infection at any time during pregnancy, and especially during the above periods, increases still further the need for blood flow and the likelihood of development of heart failure (Jenson, 1949; Hamilton, 1949, Lock, 1950, Palmer and Walker, 1949)

Fever. In general, heart rate and oxygen consumption parallel the body temperature Heart rate increases about 20 beats per minute per degree (Centigrade) of fever. The increased rate seems to be largely a direct effect on the sinoatrial node In heart block the heart rate increases only about 8 4 beats per minute per degree Centigrade (Altschule and Freedberg, 1945). Oxygen consumption increases about 10 per cent per degree of fever (Green *et al.*, 1943)

During fever induced by intravenous injection of pyrogenic substances, three stages with distinctive circulatory characteristics may be noted In the prodromal stage, immediately following injection of the pyrogen, there are no appreciable changes. A stage of chilling follows in which the cutaneous blood vessels are markedly constricted and cardiac output is below normal, both of these conditions tend to conserve body heat. The latter stage may be associated with muscle rigor which increases heat production and oxygen consumption. Muscular rigor is relatively greater in adrenalectomized animals maintained on desoxycorticosterone than in normal animals (Grant and Hirsch, 1950) A stage of flushing follows in which the cutaneous blood vessels are markedly dilated, cardiac output, heart rate, stroke volume, and oxygen consumption are elevated above normal, and sweating may ensue. Body heat begins to be lost as rapidly as, or more rapidly than, it is produced In normotensive subjects the decreased peripheral resistance and the increased cardiac output balance, so that systemic arterial pressure remains about normal In hypertensive subjects, however, systemic arterial pressure may fall due to an inadequate increase or even a decrease in cardiac output (Bradley *et al*, 1945). During the stage of defervescence the cardiac output, body temperature and cutaneous blood flow return to normal (Altschule and Freedberg, 1945, Daily and Harrison, 1948, Prec *et al.*, 1949)

Enlargement of the heart was noted by roentgenographic examination in 8 of 15 patients with neurosyphilis studied during fever therapy produced by intravenous injection of typhoid vaccine. The enlargement increased progressively during the course of therapy. Of 24 patients who had undergone fever therapy, 4 showed cardiac enlargement for as long as six months following hyperpyrexia During the course of treatment, inversion of T waves or slight depression of the diastolic base line were noted but these changes were transient. At the completion of treatment, the hemoglobin concentration and hematocrit reading had usually fallen, a few patients showed an increase in blood volume; the plasma protein concentration was lowered slightly or significantly in all patients but the cardiac output was within normal limits. No differences were noted in the electrocardiogram, cardiac output, blood proteins or hemoglobin between those patients who did and those who did not develop cardiac enlargement, and no other cause was found for the enlargement (Weens and Heyman, 1946).

During fever induced in experimental animals by radiant heat, oxygen consumption increased to about 150 per cent of normal at 42 C.; cardiac output decreased to 82 to 37 per cent of normal; arterio-

venous oxygen difference increased from an average of 6.1 to around 11.3 volumes per 100 ml. blood, systemic and pulmonary arterial pressures remained constant; heart rate increased; and right atrial pressure declined (Prec *et al.*, 1949).

Hyperthyroidism. Thyrotoxicosis results from excessive production of the internal secretion of the thyroid gland The increased secretion stimulates the metabolic rate of most organs of the body except the brain (Sokoloff *et al.*, 1950), and increases the need for blood flow which may be as much as 50 per cent above normal at rest. The disproportion may be even greater during exertion (White, 1944). The demand for increased blood flow results in an increase in heart rate, stroke volume and cardiac output, a slight increase in mean arterial pressure and a considerable widening of the pulse pressure. The increased work demand leads to cardiac dilation and hypertrophy. Atrial fibrillation frequently accompanies thyrotoxicosis and, when it does, it adds to the burden on the heart (Griswold and Keating, 1949). The thyroid secretion also acts specifically on the heart itself, directly stimulating its metabolism. The condition may be severe enough to lead to congestive failure, especially in the presence of valvular vascular deformities or when atrial fibrillation develops. The presence of thyrotoxicosis makes it exceedingly difficult to control, by digitalis, the rapid ventricular rate in patients with atrial fibrillation.

Exercise. Physical exertion induces the greatest possible increase in cardiac output. The increased output is due both to a faster heart rate and to an augmented stroke volume. In subjects in good physical condition, the latter is the more important. The systemic arterial systolic pressure and the pulse pressure increase and the diastolic pressure remains relatively constant. The arteriovenous difference in oxygen content usually increases slightly (Bruce *et al.*, 1949a, b). In the injured heart the increased venous return and the increased demand for output may readily exceed the capacity of the heart, leading to ventricular dilation and failure (see Heart Failure, page 238). In the normal subject prolonged heavy exertion apparently does not lead to significant dilation, but evidence exists that in such individuals the heart may hypertrophy (Abrahams, 1946). The work of the heart may be increased less by moderate exercise than by anxiety (Stevenson *et al.*, 1949).

Meals. Ingestion of a large meal increases cardiac output and heart work 30 to 40 per cent. The increase begins almost immediately and is maintained three or more hours. A high protein meal causes the greatest increase. Carbohydrate causes a lesser increase which is of shorter duration; fat causes a still smaller increase in cardiac output, but the output remains elevated for a longer period of time. Ingestion of 1200 ml. of water may increase cardiac output 15 to 25 per cent (Grollman, 1932).

Increased Cardiac Output in the Absence of Elevated Metabolic Rate. *Arteriovenous fistulae* Arteriovenous fistulae frequently develop as a result of trauma, gunshot or knife wounds involving the femoral or abdominal vessels. The flow through the shunts greatly augments the venous return and the cardiac output and decreases the arteriovenous oxygen difference to less than normal. When the cardiac output is large enough, hypertrophy develops. The degree of hypertrophy is directly related to the size of the fistulous opening and to the proximity of the opening to the heart. The hypertrophy is at least partially reversible when the shunt is closed (Shumacker and Stahl, 1949, Bradshaw, 1950).

Occlusion of the shunt, by application of external pressure, in man, causes immediate reduction in cardiac output and, conversely, cardiac output increases within

1 or 2 beats after re-establishing the shunt This suggests that arterial pressure, *per se*, plays an important part in regulating the stroke volume of ejection of the left ventricle. The central venous pressure tends to remain constant during opening and closing of the shunt. While systemic arterial pressure tends to fall when the shunt is opened, the fall to a considerable extent is compensated by the increased cardiac output and by peripheral vasoconstriction (Stead and Warren, 1947, Van Loo and Heringman, 1949)

Failure of development of hypertrophy in dogs, after creation of a fistula between carotid artery and jugular vein, has been reported It was concluded that dogs compensate more efficiently than rabbits which did develop hypertrophy by this procedure (Wipf and Brawner, 1949). However, it is likewise possible that the actual fistula created was smaller than the authors estimated it to be Creation of a sufficiently large fistula in dogs is difficult, but some investigators have been successful in producing fistulae large enough to cause hypertrophy (Bradshaw, 1950).

Osteitis deformans Paget's disease of bone This condition is characterized by increase in thickness of the walls of the skull, pelvis, limbs and spine, with greater content of organic tissue and calcium, but with normal amounts of phosphorus. It is associated with increased cardiac output, amounting at times to as much as 13 liters per minute, because of increased flow through the bones, and is often accompanied by a pronounced degree of arteriosclerosis (Best and Taylor, 1950) Like pregnancy, this condition is closely analogous to arteriovenous fistula.

Stress of life. Neurocirculatory asthenia Anxiety. As a part of the reaction to stressful situations of life, especially in persons who are subject to tension, frustration, conflict, anxiety and depression, the cardiovascular system may react dynamically Usually these reactions in such subjects at rest are of the hyperdynamic type that is characteristic of the normal response to exercise, they occur more in response to threatening than to actual assault upon the organism Occasionally, hypodynamic reactions occur, particularly in healthy individuals, when they feel depressed by some environmental situation. The hyperdynamic responses include fluctuations in rate and rhythm (such as paroxysmal tachycardia) and in strength and amplitude of cardiac contraction (increased stroke volume). The condition is characterized by an increase above normal in cardiac output (cardiac index averaged 5 5 with a normal output of 3.3 l /min /sq M.) despite a normal rate of oxygen consumption (Stead *et al*, 1945). In consequence, the arteriovenous oxygen difference is reduced from the normal of 4 to an average of 3.2 ml per 100 ml of blood Alterations are seen in the electrocardiogram, such as decreased amplitude or inversion of the T waves, which are similar to those which may occur in patients during coronary insufficiency (Starr and Jonas, 1943, Wolff, 1950, Stevenson *et al*, 1949)

HYPOXIA

Respiratory Hypoxia. *Low atmospheric oxygen tension* During onset of hypoxia induced by breathing mixtures of nitrogen and oxygen of less than normal oxygen content, arterial blood pressure, cardiac output and heart rate increase (Rougier and Cabanes, 1949), but the oxygen uptake by the lungs remains constant. If the oxygen content of the inspired air is lowered progressively, cardiac failure ultimately ensues with rapid decline in arterial pressure, decrease of oxygen uptake and dilation of the heart (Brofman and Green, 1943; Feldman *et al.*, 1948). Coronary blood flow increases remarkabl response to respiratory anoxia, p

cardiac failure (Green and Wegria, 1942).

Contrary to general opinion, Graybiel and associates (1950) found the size of the heart to be decreased in all normal subjects during partial acclimatization to high altitude, because of decreased filling. However, they state that life-long residents at high altitudes have hearts larger than normal

Gassing by pulmonary irritant Phosgene poisoning leads to pulmonary edema, which in turn, causes lowering in oxygen saturation of the arterial blood. The latter is the primary cause of death. Accompanying phenomena are prolonged pulmonary circulation time, increased arteriovenous oxygen difference, hemoconcentration, decreased blood volume and increased blood viscosity However, systemic venous and right ventricular pressures tend to remain constant or to fall, suggesting that a considerable vascular reserve exists in the pulmonic circuit which eliminates right heart embarrassment as an important complication of gassing (Patt *et al.*, 1946)

Anemia. In anemia, whether normochromic, hyperchromic or hypochromic, symptoms are produced which are more or less proportional to the oxygen-carrying power of the blood. No consistent changes in cardiac output are noted when the hemoglobin is above 7 grams per 100 ml. Below this level cardiac output is increased, the arteriovenous difference in oxygen content and the peripheral resistance are reduced, but right atrial pressure is unchanged (Brannon *et al*, 1945). In severe anemia (hemoglobin content below 25 per cent of normal), right atrial pressure, cardiac output, stroke volume, heart rate and pulse pressure are greatly increased, even at rest, despite reduction of blood volume to as little as 2 liters (McMichael *et al*, 1943; Sharpey-Schafer, 1944). The heart may become extremely dilated with functional insufficiency of the mitral and tricuspid valves and the appearance of "hemic" murmurs (Hunter, 1946); congestive failure may develop. The electrocardiogram in severe anemia frequently shows signs of relative myocardial anoxia, *i.e.*, flattening and inversion of T waves, elevation of diastolic base line and a tendency to low amplitude in the QRS complexes (White, 1944). In experimental anemia in dogs, the threshold for production of atrial fibrillation is reduced significantly in the presence of anemia (Horlick and Surtshin, 1949).

Stagnant Hypoxia. Shock. It is not within the province of this book to discuss the causes of and the dynamic changes in shock. These have been covered in various reviews (Moon, 1938, 1942; Blalock, 1940, 1942, Harkins, 1941, Wiggers, 1942, 1947b, 1950; Gregersen, 1946; Green, 1947). I feel that all forms of true or "irreversible" (Wiggers) shock (such as traumatic, posthemorrhagic, hypotensive and thermal) go through an initial stage of decreased blood volume, leading to decreased cardiac output and extreme arteriolar vasoconstriction (both neurogenic and humoral in origin). Ultimately these changes lead to such severe tissue anoxia that capillary damage with resulting dilation, increased permeability and stagnation occur in the capillaries.

Opdyke and Wiggers (1946) recorded right and left ventricular pressure curves during the development of post-hemorrhagic hypotensive shock. They did not find evidence of impaired myocardial contractility. However, Wiggers (1947a) felt that he had obtained evidence that the heart also appears to suffer from the decreased arterial pressure and resulting reduced coronary blood flow during hypotension resulting from hemorrhage. This is suggested by the rise of effective venous and initial ventricular pressures above normal and the failure of arterial pressure and stroke volume to recover rapidly when

blood is infused after a period of prolonged hypotension produced by bleeding Because of the possibility that impaired myocardial contractility may contribute to the frequent failure of transfusions to benefit shock (Wiggers, 1945), Page (1947) has suggested the use of intra-arterial blood transfusion in combating shock. Master and associates (1950) reported on 103 patients with acute, moderate and severe hemorrhage Fifty-seven per cent of these presented clinical or electrocardiographic evidence of acute coronary insufficiency, usually associated with a shock-like state and hypotension, the average fall in blood pressure in the group with signs of coronary insufficiency was 27 mm Hg, as contrasted to 9 mm. Hg in the group without signs of coronary insufficiency.

The impaired myocardial contractility resulting from loss of blood volume may be caused by reduced coronary blood flow during the period of hypotension This reduced flow appears to result solely from the fall in arterial pressure since, in contrast to most other regions of the body, reduced resistance to flow in the coronary vessels is found during the period of hypotension This reduced resistance persists during the period of restoration of arterial pressure which follows reinfusion of the withdrawn blood. The resistance to coronary flow is reduced even more during the secondary decline in arterial pressure in the stage of true shock (Opdyke and Foreman, 1947)

Histotoxic Hypoxia. Cyanide Poisoning. Intracoronary artery injection of sodium cyanide causes marked coronary arteriolar dilation and increase of coronary blood flow (Green and Wegria, 1942). When injected intravenously in man, sodium cyanide in doses of 0 1 to 0 2 mg per kilogram, caused a sinus pause of 0.88 to 4 2 seconds followed in some cases by nodal escape The pause immediately preceded or accompanied the respiratory stimulation. Sinus irregularity and slowing of the heart rate then ensued, followed by a gradual acceleration above control levels Electrocardiograms, recorded from four subjects executed by inhalation of hydrocyanic gas, showed initial high rates of 102 to 166, followed by cardiac slowing, with accompanying sinus irregularity and eventually complete disappearance of P waves. During a secondary increase in rate, P waves reappeared irregularly but these were always associated with A-V dissociation Later, slowing again occurred with normal A-V conduction or various forms of block. The QRS complex showed marked changes in voltage and form The T waves appeared progressively earlier so that eventually they began on the descending limb of the R wave (Wexler *et al*, 1947) The T wave changes resemble those of hypopotassemia and hypercalcemia (see page 225)

Disturbances Affecting Primarily the Heart

INFECTIONS

Myocarditis. Mild damage to heart muscle has been reported with subacute bacterial endocarditis, syphilis, scarlet fever, pneumonia and a variety of other infectious diseases (Fine *et al*, 1950) In these diseases autopsy evidence of myocardial necrosis is rare but not uncommonly the electrocardiogram may reveal wide, inverted T waves in lead I or II, prolonged atrioventricular conduction or varying grades of intraventricular block and significant RS-T deviations (Fine *et al*, 1950) Virus infections rarely cause myocardial damage but electrocardiographic changes similar to the above, and cellular infiltration with necrotizing changes in the myocardium, have been described in a case of poliomyelitis (Boucek *et al.*, 1949).

Invasion of the myocardium has been noted with trichinosis (Gould, 1945,

arz, 1947) and trypanosomiasis and these may lead to myocardial weakness or, rarely, to failure and may cause electrocardiographic changes similar to those noted in the above-mentioned acute infections.

Rheumatic fever and occasionally scarlet fever cause acute myocardial weakness which may lead to cardiac dilation and death from subacute heart failure with associated engorgement of the liver and abdominal viscera but apparently with minimal dyspnea. The patient may experience mild precordial discomfort or occasionally may have actual angina and palpitation Physical examination may reveal *murmurs which usually, in the acute stage,* are caused by functional valvular insufficiency resulting from the cardiac dilation, but these changes are relatively uncommon in young adults (Sokolow, 1948). Murmurs may of course also be present because of structural damage from previous attacks of rheumatic fever, since recurrent attacks of this disease are common The electrocardiogram may show sinus tachycardia, premature beats, prolonged P-Q interval (0 21 to 0.25 sec) atrial fibrillation, intraventricular block and either left or right axis deviation (White, 1944). The Q-T interval, corrected for heart rate, is slightly longer than normal in the presence of rheumatic carditis. However, because of variations produced by associated pericarditis, hypertrophy and other conditions, only minimal reliance can be placed on the finding as a guide in the care of the patient (Abrahams, 1949; Craige *et al.*, 1950). T_1, T_2 or T_4 is inverted in 35 per cent. Serial records are necessary (Sokolow, 1948).

More commonly acute infections, and particularly diseases such as Rocky Mountain spotted fever, typhus fever and typhoid fever, are associated with peripheral circulatory failure or what might be called medical shock. In these diseases the impairment of cardiac output results from decrease of effective blood volume caused by increased capillary permeability and stasis rather than direct impairment of myocardial contractility (Harrell and Aikawa, 1949).

Pericarditis. Acute pericarditis may lead to acute inflammatory changes usually involving the epicardium and the outer layers of the myocardium. The pericarditis may result in effusion and thus produce acute compression (see page 208), or it may ultimately cause chronic cardiac constriction through contraction of scar tissue (see page 209). Acute fibrinous pericarditis occurs most often during acute rheumatic fever, *but may accompany upper respiratory* infections, pneumonia, influenza, tonsillitis, tuberculosis and uremia, and at times may occur without apparent cause Chronic cardiac compression due to acute pericarditis has occasionally been reported (see page 209). Other characteristics that help to distinguish pericarditis from coronary occlusion are as follow: (1) Fever, a friction rub and an increased sedimentation rate tend to occur on the first day with acute pericarditis (Levy and Patterson, 1950), (2) pain is usually present (in 46 of 50 cases reported by Carmichael *et al*, 1951), but *its location in pericarditis* is highly variable, and it is intensified by respiration, cough or change of position, (3) the myocardial damage in pericarditis is diffuse, whereas in infarction resulting from arterial occlusion it is sharply localized; as a consequence, in the electrocardiogram shifts in the diastolic base line tend to be "reciprocal" in leads I and III in occlusion but not in pericarditis, (4) a Q wave develops rapidly in the leads in which an electrode lies over the infarcted area, whereas Q waves are not produced with pericarditis (Myers, 1950).

The electrocardiogram may simply show decreased voltage if effusion is the main manifestation. More commonly (60 to 80 per cent of cases) changes are described

which are considered specific for pericarditis. These changes include depression of the diastolic base line in all three limb leads (I, II and III), and in CF_2 and CF_4 during the first 10 days. During the ensuing days, the electrocardiograms show return of the diastolic base line to the isoelectric line and appearance of inverted T waves in most leads. The latter is followed by return to normal in from four days to seven weeks (Bellet and McMillan, 1938; Nay and Boyer, 1946, Logue and Wendkos, 1948) The consensus seems to be that the electrocardiographic changes result from myocardial injury This injury may be in the form of subepicardial myocarditis (Burchell *et al.*, 1939) or may be caused by impaired coronary blood flow as a result of elevation of pericardial or intramyocardial pressure. Among patients who died it was noted that shift of the diastolic base line had been present in the electrocardiogram only in instances in which microscopic examination of the heart revealed myocardial damage (Bellet and McMillan, 1938).

Endocarditis. In a survey of 76 fatal cases of subacute bacterial endocarditis (Saphir *et al*, 1950), various combinations of inflammation, perivascular infiltration, Aschoff bodies, infarcts and intravascular emboli were found in the myocardium. Electrocardiograms were available in all cases. The most significant findings were revealed when the electrocardiograms were taken seriatum In 33 cases, low voltage was seen which the authors attributed to diffuse involvement Left axis shift was seen in 36 and right axis shift in 20 instances. Slight notching and other changes of the P wave were seen in 8 cases. Elevation of the diastolic base line was present in 35 and inverted T waves in a similar number of instances, in 19 of these the change could not be attributed to digitalis or to pre-existing disease. Tachycardia, presumably due to fever, was present in 23, and various types of premature beats in 23 instances Twelve patients showed atrioventricular conduction delay, and intraventricular block was present in four Seventy-five per cent of the 61 patients in whom serial electrocardiograms were taken showed progressive changes. The authors felt that the correlation between electrocardiographic and autopsy findings was close enough so that the electrocardiogram could serve to present valuable evidence of the presence of anatomic changes

MECHANICAL DISTURBANCES

Trauma. Demonstrable evidence of cardiac damage was found in 76 per cent of 42 cases of rather serious accidental injuries to the body. The myocardial damage was associated in some instances with no symptoms and in other cases with precordial discomfort or slight dypsnea. In many instances gallop rhythm, pericardial friction rub and various systolic murmurs were noted momentarily In a few instances the electrocardiograms showed evidence of pericardial or myocardial involvement but in only one instance was damage permanent Death occurred in one person Changes noted in the electrocardiogram included slight depression of the diastolic base line, elevation of the T wave in one or more leads, or flattening or inversion of the T waves, shift of the electrical axis, and bundle branch block (Sigler, 1945). In another series of 75 patients, abnormal electrocardiograms were noted in 20. The abnormalities included paroxysmal tachycardia, and flattening or inversion of the T waves in leads I and II (Barber, 1944)

Funnel Chest. Funnel chest or pectus excavatum may be hereditary or, rarely, may follow injury It results from posterior displacement of the sternum in relation to the lower anterior chest wall which maintains its normal position. In a series of 9 persons with funnel chest, none experienced any serious cardiac embarrassment,

though several noted palpitation and dyspnea after exercise. Electrocardiographic abnormalities were minor and were explainable on the basis of a combination of shift to the left and rotation of the heart on its long axis. Treatment is considered to be rarely indicated (Teplick and Drake, 1946).

METABOLIC DISTURBANCES

Hyperthyroidism. For the effects of hyperthyroidism on the body as a whole, see page 218 Hyperthyroidism increases the sensitivity of the heart to sympathetic stimulation and decreases its sensitivity to vagal stimulation. In hyperthyroid rabbits, cats and rats (thyroxin administration), peripheral vagal stimulation caused less slowing of the heart than in normal animals, and occasionally vagal stimulation caused acceleration. Normal cardiac slowing was restored by administration of eserine or rostigmine. In perfused isolated hearts from hyperthyroid animals, acetylcholine had only a slight depressor action which was always followed and overshadowed by a pronounced stimulation similar to that produced by epinephrine. Unusually high amounts of an epinephrine-like substance appeared in the perfusate from such hearts following injection of relatively small doses of acetylcholine. Perfused hearts from hyperthyroid animals were also shown to react with increased frequency and amplitude to doses of epinephrine approximately one-fifth that required for hearts from normal animals (Hoffmann *et al*, 1947). This change in sensitivity to epinephrine probably accounts in part for the tachycardia in hyperthyroidism.

Hypothyroidism. Myxedema in man is characterized by low basal metabolic rate, pulse rate, plasma volume, velocity of blood flow and vital capacity (Blumgart *et al.*, 1930). Venous pressure is approximately normal. The cardiac output and the work of the heart are decreased below normal, the decrease being relatively greater than that of the oxygen consumption, so that the arteriovenous oxygen difference is above normal (Altschule and Volk, 1935). The heart is generally enlarged and the mean arterial pressure is slightly elevated but the pulse pressure is less than normal. With treatment the heart decreases in size, the mean arterial pressure usually declines and the pulse pressure widens. Pericardial effusion may be present (Harrell and Johnson, 1943).

Blood cholesterol levels are considerably elevated in hypothyroid patients, and probably related to this, the incidence and severity of atheromatous changes is greatly increased in all arteries, including those of the heart.

The electrocardiogram during the myxedematous state often shows flattening or inversion of the T wave, particularly in lead II, small P and QRS deflections and frequently left axis deviation (Lerman *et al.*, 1933). The return of the electrocardiographic pattern to normal with treatment probably results from increased muscle tone, loss of interstitial edema and disappearance of any pericardial effusion that may have been present.

Since the work of the heart in hypothyroidism is apparently decreased both at work and in exercise, creation of a mild state of hypothyroidism has been recommended in congestive heart failure. Surgery and radioactive iodine (I^{131}) and astatine (Hamilton *et al.*, 1950) have been employed to decrease thyroid function (Riseman *et al.*, 1935, Blumgart *et al*, 1950a; Gordon and Albright, 1950).

In thyroidectomized cats vagal stimulation caused more marked and more sustained slowing than normal. Isolated perfused hearts from thyroidectomized cats showed an intense depressive response to acetylcholine, and a weak stimulative response to epinephrine. Epinephrine-like substances appeared in the perfusate from

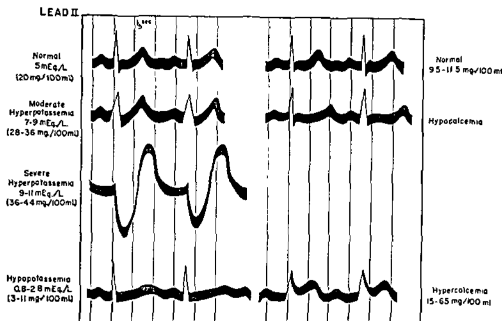


Figure IV-12. Schematic diagram of changes in electrocardiogram resulting from abnormal concentration of electrolytes

such hearts only when high doses of acetylcholine were given (Hoffmann *et al.*, 1947). On the basis of these results, the authors conclude that the bradycardia of hypothyroidism is caused by "changes of sensitivity of the adrenergic and cholinergic heart effectors to the respective neurotransmitters."

Disturbances of Plasma Electrolyte Levels. *Hyperpotassemia.* When potassium chloride is injected intravenously into dogs under barbital anesthesia, death occurs at an average plasma concentration of about 15 mEq./l (12-20 mEq./l). Electrocardiograms (lead II) show initially an increase in the amplitude of the T wave until intraventricular block occurs. Skeletal muscle contractions are not appreciably affected at these levels (Winkler *et al.*, 1939).

In man, hyperpotassemia has been produced by administration of 2 to 6 Gm of potassium iodide per day, in the treatment of syphilis and in patients with uremia. Serum potassium levels as high as 10.5 mEq./l have been recorded (normal about 5 mEq./l.) during which time the patient may develop acute uremia with oliguria, recurrent nausea, episodes of bradycardia with symptoms of heart failure and sudden ascending quadriplegia without paralysis of trunk or disturbance of speech or mental function (Finch and Marchand, 1943). In hyperpotassemia the electrocardiograms (Figure IV-12) may show (1) elevation of T waves (at 7 to 9 mEq./l. of K), (2) decrease of R and increase of S waves, (3) disappearance of P waves (at 9 to 9.5 mEq./l.), (4) S-T take-off from S so that S-T segment appears depressed, and (5) spread of QRS and T until they form smooth diphasic QRST complexes (at 9.5 to 10.5 mEq./l. of K) (Finch *et al.*, 1946). Also noted in the electrocardiograms are: sinus tachycardia, supraventricular paroxysmal tachycardia and complete A-V dissociation with irregularities suggesting ventricular fibrillation (Stewart and Smith, 1941, Keith *et al.*, 1944, Stewart *et al.*, 1948).

Hypopotassemia. Marked lowering of serum potassium from the normal of about 20 mg./100 ml (5 mEq./l.) to 3 to 11 mg./100 ml. (0.8 to 2.8 mEq./l.) occurs during the attacks in family periodic paralysis,

and as a result of loss of potassium in chronic nephritis, in overtreatment of adrenal cortical insufficiency with desoxycorticosterone and occasionally during treatment of diabetic acidosis. Clinical symptoms accompanying the hypopotassemia include skeletal muscular weakness and paralysis which are more marked in the lower extremities and are accompanied by pain and stiffness in the muscles. Potassium excretion is not increased during the attacks of periodic paralysis, the attacks subside spontaneously. The electrocardiograms in hypopotassemia characteristically show rounded, widened T waves of low amplitude which prolong the Q-T interval and shorten the S-T segment. U waves are prominent (Stewart *et al*, 1940b, Stoll and Nisnewitz, 1941, Brown *et al*, 1944; Ernstene and Proudfit, 1949, and Myers, 1950). (See Figure IV-12.)

Changes resembling hypopotassemia produced by desoxycorticosterone. Necrosis of myocardial fibers by repeated injections of desoxycorticosterone and replacement by fibroblasts is produced in rats. The lesions cannot be distinguished from those produced by diets low in potassium. The cardiac potassium concentration is not consistently lowered by the desoxycorticosterone but the lesions can be prevented by addition of potassium chloride to the drinking water during the period of desoxycorticosterone administration (Darrow and Miller, 1942).

Hypocalcemia. Hypocalcemia causes prolongation of the Q-T interval with lengthening of the S-T segment (Ernstene and Proudfit, 1949) and low T waves in lead I and/or lead II (Ljung, 1949). (See Figure IV-12.)

Hypercalcemia. Electrocardiograms taken during continuous intravenous infusion of calcium chloride into morphinized or barbitalized dogs reveal an initial phase of cardiac slowing frequently associated with widening of the QRS complex and of the T wave so that the T begins to take off from the QRS. In addition, various degrees of A-V block and atrial fibrillation are observed. These changes occur at calcium concentrations ranging from 15 to 65 mg / 100 ml. With continuing infusion this phase is succeeded by a phase of rapid heart rate with frequent isolated premature beats which is followed by tachycardia and then by ventricular fibrillation or cardiac arrest, at calcium concentrations of 70 to 190 mg./100 ml. (Hoff *et al.*, 1939). Atropine decreases the A-V delay and atrial fibrillation but promotes the development of ventricular premature beats, presumably by blocking the vagal fibers Narcotic doses of sodium amytal suppress all cardiac irregularities and prevent arrest of the heart (Hoff and Nahum, 1937). (See Figure IV-12.)

Elevated levels of magnesium. Magnesium injected intravenously into unanesthetized dogs, at levels below 5 mEq./l, causes an initial drop in arterial pressure, followed by depression and failure of respiration at levels of 15 to 17 mEq./l If the animal is kept alive by artificial respiration, further increase in magnesium to 27 to 38 mEq./l. leads to progressive slowing, lengthening of the P-Q interval (to as much as 0.30 sec.), various types of heart block, widening of the QRS complex and finally to cardiac arrest. Cardiac arrest never precedes respiratory arrest (Smith *et al.*, 1939a, b).

Thiamine Deficiency. Beriberi Heart. Among the early descriptions of beriberi heart disease is that of Wenckebach (1934). He emphasized the presence of cardiac enlargement, particularly on the right, associated with a jumpy pulse of increased frequency, frequent occurrence of syncope, pistol-shot sounds over the large arteries, and hardness and swelling of the calf muscles.

Blankenhorn (1945) has given the following criteria for the diagnosis of beriberi heart disease: enlarged heart with normal sinus rhythm, dependent edema, elevated venous pressure, peripheral neuritis or pellagra, nonspecific changes in the electrocardiogram, no other cause of heart disease evident, gross deficiency of diet, and finally improvement with use of thiamine He feels that the cardiovascular aspects of beriberi primarily result from the myocardial disturbance caused by the thiamine deficiency

In a subsequent paper Blankenhorn and associates (1946) reported that they had seen beriberi heart disease based upon the above criteria in 0 1 per cent of all medical admissions in the previous five years Of this group of 12 patients, five died in the hospital or within one to three months and in only one was the response to thiamine dramatic. Eleven of these patients had dependent edema, and the venous pressure was elevated in nine of them, the venous pressure being increased above normal by 10 to 29 cm. of H_2O. Electrocardiograms made in 10 of the 12 patients, showed heart rates above 90 in six, prolonged P-Q interval in two, low voltage of T and/or QRS in seven, and bundle branch block in one. Marked changes were noted in the electrocardiograms in five of these patients as they improved (See also Gutenkauf, 1951)

Wallace and Clark (1949) reported that patients with thiamine deficiency and Wernicke's syndrome (hemorrhagic polioencephalitis superior), but without symptoms of heart failure, had electrocardiograms with low T waves in lead I, and inverted T waves in leads II and III. The T waves became almost normal after six days of active therapy with thiamine and were completely normal within 20 days.

In pigs the outstanding cardiac symptoms of acute thiamine deficiency were exertional dyspnea, occasional cyanosis and collapse. Electrocardiograms showed bradycardia, prolonged atrioventricular conduction time, occasional dropped beats and occasional premature beats. At autopsy the hearts showed focal necrosis in the atria and ventricles (Wintrobe, 1946) Rats, in addition, showed atrial fibrillation, A-V nodal rhythms, sinus arrest, widened QRS complexes, and increased height and widening of P and T waves (Hundley *et al*, 1946).

In five dogs rendered deficient to vitamin B_1, inversion of T waves and neurologic signs were noted In three dogs evidence of outpouring of pyruvate by the heart was obtained by analysis of samples of blood simultaneously obtained from the femoral artery and the coronary sinus. No such outpouring was noted in three other dogs that were placed on a thiamine-deficient diet, they did not show electrocardiographic changes despite elevation of their general blood levels of pyruvate (Randles *et al*, 1947).

Hypothermia. In dogs and guinea pigs, lowering of body temperature towards lethal levels (from 38 to 14 C.) gradually slows the heart rate and the atrioventricular conduction rate. After an initial rise during shivering (38 to 25 C.), the arterial pressure falls. The electrocardiograms at very low body temperatures show irregularities, and, at still lower temperatures, atrioventricular block or obliteration of the P waves and nodal rhythms (Crismon, 1944). The ventilation rate remains high relative to the oxygen uptake until body temperature reaches 21 to 17 5 C, when respiratory failure occurs Above these latter temperatures, however, external respiration is adequate (Gosselin, 1949). In addition, Lange and associates (1949) noted, in the electrocardiograms, lowering and inversion of the T waves and depression or elevation of the diastolic base line

in various leads. These two types of change were reversed by administration of oxygen under pressure and were, therefore, considered to be due to anoxia.

Blood viscosity increases two to threefold between 39 and 20 C., principally because of hemoconcentration (hematocrit reading at 39 C. is 43.9 ± 8.62, and at 20 C., 60.6 ± 5.60). Systole and isometric relaxation, and the Q-T interval of the electrocardiogram are prolonged progressively (six- to seven-fold increase at 18 C.) while the systole-to-cycle ratio tends to remain constant with cooling. Death is considered to be cardiac in origin and to be caused by inadequate coronary flow and diminished metabolic rate. These changes occur whether or not artificial pulmonary ventilation is given (Hegnauer *et al.*, 1950).

TOXIC EFFECTS OF DRUGS

Digitalis. *Cardiovascular effects of digitalis.* Administration of digitalis to the patient with heart failure improves the circulation by increasing the cardiac output and the velocity of the circulation (Movitt, 1946; Harvey *et al.*, 1949, Ferrer *et al.*, 1950). These in turn lead to salt-and-water diuresis, reduction of blood volume and systemic venous pressure and relief of dypsnea, edema and other symptoms.

Tepper (1950) noted the effect of intravenous strophanthin on venous pressure, arterial pressure, heart rate and respiration in three groups of patients. In patients without heart failure no significant changes were observed. Both in patients with right heart failure and in those with left heart failure, pulse rate and arterial diastolic pressure declined. In those with left heart failure, systemic venous pressure increased markedly and respiration became slower and deeper. In those with right heart failure, systemic venous pressure fell an average of 5 cm. of H_2O. He proposed that these two types of response could be used as a differential test between right and left heart failure. (See also Cournand, 1950, for similar effects of Digoxin in right heart failure associated with chronic cardiopulmonary diseases.)

In patients with clinical congestive heart failure resulting from non-valvular types of heart disease, ouabain was given by intracardiac administration in doses of 0.25 to 0.75 mg. This substance caused increases in both systemic and pulmonary arterial systolic and pulse pressures which were associated with increased stroke volume and cardiac output per minute. The results were best explained by a direct action of the ouabain upon the contractility of the myocardium (Bloomfield *et al.*, 1948).

Effects of digitalis on the myocardium. It has been postulated by Dock and Tainter (1930) that digitalis produces its effects by damming blood in venous reservoirs, particularly in the liver. However, the present consensus seems to be that the drug acts primarily by increasing the functional capacity of the heart (Bloomfield *et al.*, 1950). The improved capacity in large part results from improved myocardial contractility. The improved contractility is manifested by ability of the myocardium to do a greater amount of work at a given initial length (Cattell and Gold, 1938) or, conversely, by its ability to assume a shorter initial length if the work remains unchanged. The improved cardiac action also results from greater and more prolonged systolic shortening and at the same time more complete filling of the ventricles in diastole (Krantz and Carr, 1949). The effects of digitalis are not seen in the normal myocardium but become evident in failing muscle (Sciarini *et al.*, 1948). For a detailed discussion of the effects of the cardiac glycosides on the energy metabolism of the normal and the failing heart, see Wollenberger (1949).

Effects of digitalis on heart rate. Cardiac slowing produced by digitalis, particularly in the presence of atrial fibrillation,

also aids in improving cardiac efficiency Slowing of the heart rate by digitalis represents in part the effect of the drug on the chemoreceptors in the carotid body, which in turn reflexly induces a vagal discharge that inhibits the sinoatrial node and prolongs the refractory period of the atrioventricular node. This effect is blocked by atropine. The drug also directly affects the sinoatrial node to cause slowing of impulse initiation and directly prolongs the refractory period of the atrioventricular node, since atropine does not prevent cardiac slowing with larger doses of digitalis This mechanism is particularly important in slowing the ventricular rate during atrial fibrillation (Movitt, 1946) However, the rise in cardiac output when Digoxin is given in heart failure is apparently as pronounced in patients with normal rhythm as in those with atrial fibrillation, and is not correlated with either the initial heart rate or the degree of cardiac slowing produced by the drug (Kelly and Bayliss, 1949). Digitalis occasionally has an antifibrillary effect which may be attributed to the increase in refractory period or to the relief of dilatation resulting from the inotropic effects of the drug (DiPalma and Schultz, 1950). The drug appears to have no effect on the coronary vessels (Krantz and Carr, 1951; Bing *et al*, 1950).

Effects of therapeutic doses of digitalis on the electrocardiogram Within the therapeutic range, digitalis causes a number of changes in the electrocardiogram which need to be distinguished from those resulting from coronary occlusion. The more important electrocardiographic changes include shortening of the Q-T interval, prolonged atrioventricular conduction (increased P-Q interval), changes in the S-T segment and T waves, and mild disturbances of rhythm The T waves tend to become inverted and the S-T segment, while taking off close to the diastolic base line, frequently slopes gradually upward or downward and ends in a more abrupt return to the diastolic base line. Unlike the pattern in coronary occlusion, the apex of the T wave is directed away from, rather than towards, the diastolic base line The effects noted suggest that digitalis has increased the speed of recovery of portions of the myocardium so that the duration of the period of depolarization is equal in all parts As a consequence, the whole heart tends to behave electrically like a single strip of muscle. For effects of Digitoxin on the V leads, see Beers and associates (1951) The latter workers noted changes similar to those described above, but in a few patients the T waves tended to become tall and pointed in the left precordial leads

Effects of toxic doses of digitalis In toxic doses, digitalis tends to cause anorexia, nausea, vomiting, diarrhea, abdominal discomfort and restlessness, blurred, yellow vision, mental confusion, disorientation and psychoses The heart may show abnormally prolonged atrioventricular conduction (more than 0.2 second), dropped beats, and even complete atrioventricular block, premature beats, particularly of ventricular origin, bigeminal or trigeminal rhythm, see Cardiac Irregularities, page 178), atrial, nodal or ventricular tachycardias, or atrial or ventricular fibrillation. The appearance of any of these should be taken as an indication for stopping the administration of the drug (Movitt, 1946, Levine, 1948, Master, 1948, Burwell and Hendrix, 1950). Digitalis in toxic doses may lead to increasing severity of heart failure, possibly by decreasing the myocardial efficiency (Batterman and Gutner, 1950).

Question of additive toxic effects of calcium and digitalis. Since calcium and digitalis have similar effects on the heart, it has been postulated that calcium administration may potentiate the toxic effects of digitalis and *vice versa.* Administration of calcium chloride intravenously to di

talized dogs has led to death by ventricular arrest or ventricular fibrillation. However, it was found that the amount of calcium required and the blood levels reached were only slightly less than when calcium was administered alone (the differences being statistically insignificant), and that the electrocardiographic changes were identical with those of calcium poisoning (Hoff *et al*, 1939, Smith *et al.*, 1939, Blumenfield and Loewi, 1945; Friedman and Bine, 1948)

Digitalis and potassium. In tests on the embryonic duck heart, Friedman and Bine (1947) noted that absence of potassium led to arrhythmias and early cessation of beating; also that absence of potassium accentuated the effects of Lantoside C but that excess of potassium inhibited the action of the Lantoside. They concluded that, while excess of potassium itself depresses the irritability of the heart, it may serve as a source of potassium to a heart which is losing potassium after exposure to toxic amounts of digitalis

Digitalis in the presence of hyperthyroidism. An experimental study of the combined toxicity of digitalis and thyroid extract or thyroxin was carried out by Dearing and associates (1950). They found that even twice the therapeutic dose of digitalis (which gave toxic symptoms) caused only a few mild myocardial changes. Thyroxin or thyroid extract alone, in amounts sufficient to cause moderate hyperthyroidism, likewise produced no effect, though amounts sufficient to cause severe hyperthyroidism led to death in two of eight experimental animals. These two animals showed scattered zones of destruction of myocardial fibers and their electrocardiograms revealed tachycardia, tall or short and inverted T waves, and slight changes in the diastolic base line. The combination of normal, and especially of toxic doses of digitalis with moderate hyperthyroidism led to death, frequently with extensive degeneration or necrosis of myocardial fibers. In 3 animals the electrocardiograms showed ventricular premature beats, paroxysmal atrial and ventricular tachycardias, ventricular fibrillation, changes in the diastolic base line and decrease in amplitude or inversion of T waves. They did not find any electrocardiographic pattern to be characteristically associated with the myocardial lesions.

Quinidine. This drug primarily prolongs the refractory period of the myocardium, and is useful in changing atrial fibrillation to a normal rhythm and in decreasing the incidence of ventricular premature beats and fibrillation. It acts by prolonging the refractory period and slowing the rate of conduction (Levine, 1945). Its administration should always be preceded by a test dose of 0.2 Gm. If no toxic symptoms are noted within 12 hours, 0.2 Gm. may then be given every four hours, day and night. McMillan and Welfare (1947) recommend that, in treating atrial fibrillation, the dose be increased by 0.2 Gm. every 10 hours until normal sinus rhythm or toxic symptoms appear, or until a maximum dose of 0 8 Gm. every four hours is reached Fibrillation not infrequently reappears if the drug is stopped after converting a fibrillating heart to a normal rhythm In toxic doses, quinidine causes anorexia, mild nausea, vomiting, headache, drowsiness and tinnitus. McMillan and Welfare observed severe reactions in 10 per cent of their 50 patients. These included syncope, peripheral vascular collapse, pulmonary embolism, delirium and temporary asystole. Quinidine may also produce partial atrioventricular block, prolongation of the Q-T interval and slight notching of the T wave, and may even lead to ventricular fibrillation (Krantz and Carr, 1949). Inhibition of respiration has been noted in cats (Levine, 1945).

DiPalma and Schultz (1950), in their review of antifibrillatory drugs, suggest the

following in regard to quinidine. (a) The drug is strongly advised in the presence of fresh fibrillation or flutter with normal x-ray shadows, sounds and blood pressure, in ventricular tachycardia and in post-thyroidectomy flutter or fibrillation (b) It is generally accepted with relatively old flutter or fibrillation, with premature ventricular beats and with paroxysmal atrial or nodal tachycardia which fails to respond to other measures. (c) Quinidine is generally rejected in the presence of congestive failure, atrial fibrillation which has replaced angina pectoris, hyperthyroidism with sinus tachycardia, a markedly enlarged heart or severe mitral stenosis (d) It is strongly contraindicated in the presence of complete heart block, bundle branch or intraventricular conduction defect, subacute bacterial endocarditis or overdigitalization. Quinacrine shows promise of being equal to or even superior to quinidine.

Quinine. Monkeys with a severe anemia resulting from malaria caused by *Plasmodium knowlesi* succumbed to smaller doses of quinine, given intravenously, than did normal monkeys or those with a mild degree of anemia. The electrocardiograms taken after administration of quinine follow the same changes in the normal and infected animals but in the latter the tracings show greater prolongation of the P-Q and Q-T intervals and of the QRS complex (Rigdon and Ruskin, 1949) The malaria itself caused minimal changes (Ruskin and Rigdon, 1949)

Nicotinic Acid. Nicotinic acid had no effect on "normal" myocardium of isolated perfused hearts. In "failing" hearts, however, this substance caused a marked increase in amplitude of contraction and a reversal of abnormal rhythms (Calder, 1947).

Emetine. This drug is usually given intramuscularly in doses of 1 mg./Kg./day (up to a maximum of 64 mg./day) for eight to 12 days in the treatment of amebiasis (*Entamoeba histolytica*). Patients receiving this dose experience weakness and marked decrease in exercise tolerance but no change in blood pressure or heart rate They should be kept in bed during and for a short while after treatment. Charters (1950) and McMillan (1950) have noted inversion or flattening of the T waves in leads I, II and CF_4 in the electrocardiograms of some patients receiving the drug in these doses. The changes began to appear about the eighth day and disappeared during the first to fourth week after discontinuing the drug. No instances of cardiac enlargement or interference with impulse initiation or conduction were noted by these investigators However, Dack and Moloshok (1947) noted fatigue, dyspnea, tachycardia and total inversion of T waves in all leads Two of nine patients showed a deep Q in leads II and III with doses of 0 32 to 1 42 grams Two of Charters' patients had accidentally received 20 to 30 times the usual dose but only one of these showed evidence of myocardial damage (tachycardia, poor exercise tolerance and lowered arterial pressure). These symptoms disappeared after 13 weeks He also described one patient who had received 120 injections (probably over 4.8 grams of emetine over a period of four years) without toxic signs

Sulfonamides. Hafkesbring and Wertenberger (1947) report that sulfonamides, given to dogs in four daily doses of approximately 0 15 Gm/Kg each, caused slight shift of the diastolic base line relative to the isoelectric line and/or slight changes in the T waves in the electrocardiogram in seven instances among 39 tests The direction of the changes was not constant and the changes disappeared after the drug was stopped in all but two cases. They felt that these changes in the electrocardiogram were possibly the result o

morphologic changes in the cardiac muscle caused by sensitization to sulfonamide. No effect upon the conduction system was noted. Lilienfield and associates (1950) reported a case of sulfonamide sensitivity in which the patient developed tachycardia with distant sounds, a second pulmonic sound that was louder than the aortic, a pulmonic systolic murmur, a presystolic gallop rhythm, and an arterial pressure of 88/70 but no cardiac enlargement. His electrocardiogram showed left axis deviation, intraventricular conduction defect progressing to right bundle branch block, and slightly inverted T waves in leads I and II. Complete recovery ensued upon stopping the drug.

Procaine. Procaine has been administered intravenously for reducing cardiac irregularities and for relief of certain peripheral vascular disorders. Long and associates (1949) studied the potential toxic effects of this substance in dogs. They found progressive changes in the electrocardiogram as this dose was increased from 4 to 80 mg/Kg. These changes included lengthening, flattening or inversion of the T waves, lowering of the R waves, increase of the S waves, development of a "J" shape in the S-T segments, increased width of the QRS complexes, prolongation of the P-Q intervals, ventricular tachycardia and ventricular fibrillation. All except the last changes were reversible if the dogs were given artificial respiration. (See also Di-Palma and Schultz, 1950.)

Mercurial Diuretics. In the perfused isolated rabbit heart Mercuhydrin* caused prolonged atrioventricular and intraventricular conduction, prolonged electrical systole, dropped beats and cardiac asystole. In addition, Thiomerin Sodium* caused transitory ventricular ectopic beats and fibrillation and, in large doses, cardiac dilation and decreased contractility and shift of the diastolic base line. Premedication with BAL (British anti-lewisite), ascorbic acid or thiamine tended to elevate the toxic levels of mercurials These substances were, however, much less effective when given after signs of toxicity had developed (Ruskin and Johnson, 1949)

5. HEART FAILURE

Circulatory Conditions with Which Heart Failure May be Associated

RELATION OF MYOCARDIAL WORK LOAD TO HEART FAILURE

Heart failure may best be defined as the inability of the myocardium to meet the circulatory demands placed upon the heart. The circulatory demand, which may be expressed as myocardial work, is the minute output of a ventricle multiplied by the mean pressure which the myocardium must develop within the ventricle to eject this quantity of blood. The factors which lead to increased work demands upon the heart are indicated in Table IV-2. Increased pressure of ejection may be required either because of elevation of pressure in the arterial circuit or by narrowing of the orifice through which the blood must pass upon leaving the ventricle. Increased volumes of blood must be ejected in various conditions in which the demands by the tissues for blood is increased and also whenever valvular or septal defects are present which allow regurgitation of the ejected blood. Whenever the volume of blood to be ejected or the pressure required exceeds the capacity of either ventricle, heart failure ensues.

RELATION OF MYOCARDIAL EFFICIENCY TO HEART FAILURE

Failure of the heart may occur in the absence of increased work demands when

* Mercuhydrin is manufactured by Lakeside Laboratories, Inc., Milwaukee, Wisconsin; Thiomerin Sodium, by Campbell Pharmaceutical Co, New York, N. Y.

TABLE IV-2

Factors Causing or Contributing to Heart Failure

I. Mechanical overloading of heart
  A. Increased resistance to ejection of blood by left ventricle
    1. Stenosis of orifice of aortic valve or lumen of aorta
    2. Coarctation of aorta
    3. Systemic arterial hypertension (elevation of mean arterial pressure)
    4. Adhesions between ventricle and chest wall
  B. Increased resistance to ejection of blood by right ventricle
    1 Stenosis of orifice of pulmonary trunk (tetralogy of Fallot)
    2. Pulmonary hypertension resulting from
      a Pulmonary arteriolar sclerosis
      b Pulmonary emphysema
      c. Mitral stenosis
      d. Left ventricular failure
      e. Patent ductus arteriosus or persistent truncus arteriosus
  C. Excessive demand for output affecting left ventricle only
    1 Aortic insufficiency
    2 Mitral insufficiency
    3 Patent ductus arteriosus
  D. Excessive demand for output affecting right ventricle mainly
    1. Patent septal defects, particularly of atria
    2. Eisenmenger complex (ventricular septal defect with dextroposition of aorta)
  E. Excessive demands for output affecting both ventricles
    1. Arteriovenous fistula
    2 Exercise
    3. Hyperthyroidism
    4. Anemia
    5. Anoxia (all types)
    6 Excessive blood volume (as after transfusion, infusion, and overdosage with desoxycorticosterone)
    7 Fever (artificial or accompanying infections)
    8. Coughing
    9. Digestion of meals
    10 Pregnancy
    11 Ventricular septal defect
II Primary myocardial insufficiency
  A Loss of myocardial fibers
    1 Myocardial infarction
    2 Diffuse myocardial sclerosis
  B Impaired myocardial circulation
    1 Coronary insufficiency
      a Narrowing of coronary vessels
      b Excessive myocardial hypertrophy
    2 Excessive tachycardia
    3 Anoxia
      a Respiratory
      b Anemic
      c Stagnant
      d Tissue
    4 Aortic stenosis or insufficiency
  C Impaired myocardial contractility
    1 Myxedema
    2 *Thiamine deficiency*
    3 Myocarditis
III Impaired cardiac filling
  A Excessive tachycardia or cardiac irregularities
  B Adhesive pericarditis
  C Cardiac tamponade

for one reason or another the amount of energy which may be developed by the contracting myocardium is impaired (Moe and Visscher, 1939; Visscher, 1940). Conditions leading to failure are summarized also in Table IV-2.

Limitations for Myocardial Work in Nonhypertrophied Heart with Normal Blood Supply. In the nonhypertrophied heart with a normal coronary circulation, the limits in the work output of the heart are probably determined by the mass of muscle and the amount of energy which can be developed by this mass. Angina, indicative of relative myocardial ischemia or anoxia, is not seen. In myxedema and thiamine deficiency and probably in the various forms of acute myocarditis the decrease in the ability of the myocardium to meet the work demands is probably due to a decrease in the amount of energy which can be developed per gram of myocardium (Katz and Mendlowitz, 1938, Katz, 1940).

Limitations Imposed by the Coronary Circulation. Limitation of energy development by the myocardium may also be due to inadequate blood supply in coronary insufficiency, that is, narrowing without actual occlusion of the coronary vessels (Bing *et al.*, 1949) and in various forms of anoxia. These forms of anoxia are respiratory anoxias, including the cyanotic types of congenital heart disease, in which the blood is insufficiently oxygenated; anemic anoxia, such as is seen with decreased hemoglobin or red cell content and in carbon monoxide poisoning; stagnant anoxia, such as is seen after prolonged arterial hypotension (Wiggers

1947a, Page, 1947b); and tissue anoxia, such as is seen with cyanide poisoning. This cause of failure may also be seen after injection of excessive quantities of the coronary constrictor agent, pitressin (Green *et al.*, 1942). A relative myocardial anoxia may develop as a result of administration of epinephrine, since this substance may increase the oxygen consumption more than it increases the work output of the myocardium, in other words, this drug may decrease myocardial efficiency (Green *et al.*, 1942). Reduction in work output of the myocardium of course also results from necrosis of myocardial tissue following coronary occlusion Excessive increase in right ventricular pressure may seriously limit right coronary blood flow, leading to right ventricular failure (Visscher, 1939). In the presence of myocardial hypertrophy, cardiac work is usually increased at rest, but the hypertrophy is not accompanied by a corresponding increase in the blood supply As a consequence, the maximum increase in the work of such hypertrophied heart during exertion will be less than that of the normal heart.

Extra-cardiac Factors Limiting Myocardial Work. Reduction in development of energy and ejection of blood by the heart may result from cardiac tamponade or from constrictive pericarditis, both of which interfere with filling of the ventricles and may produce symptoms similar to heart failure.

RESPONSE OF MYOCARDIUM TO INCREASED WORK LOAD

Starling's Law of the Heart. Increase in the initial length of the ventricular muscle fibers increases the energy released during the ensuing systole. The increased length is brought about by augmenting the volume of blood in the ventricle at the end of diastole, and is accompanied by an increase in the initial tension, *i e.*, by an increase in the pressure in both the ventricle and the atrium at the end of diastole. The extra energy may be used by the ventricle to eject a larger volume of blood against the same arterial pressure, to eject the same volume of blood against a higher arterial pressure, or to do both. If, however, the distention of the ventricle exceeds a critical limit, its ability to eject blood begins to decrease progressively with further increase in diastolic size; the heart is then in a stage of decompensation or acute failure (Howarth *et al.*, 1946, Nylin, 1947, McMichael, 1950). The normal heart often does not increase in size with moderate increase in work, and may even decrease in size (Richards, 1949). For a discussion of the various factors that may normally affect myocardial contractility, see page 152

FACTORS LEADING TO AN INCREASED DIASTOLIC VOLUME OF A VENTRICLE

Increased Venous Return. An increased atrial pressure may be brought about by transfusions, by mobilization of blood from blood reservoirs such as the liver and spleen or by expressing blood from the muscle during exercise or by the occurrence of shunts or arteriolar dilatation. In addition, acute increase in venous return in edematous patients may occur at night because of resorption of the edema fluid As a result of the increased diastolic filling, the normal ventricle is enabled, within limits, to eject larger volumes of blood per beat. Increased left ventricular diastolic size is also brought about by regurgitation through an insufficient aortic valve; and increased right ventricular initial length, by atrial and ventricular septal defects.

Increased Resistance to Ejection. When the work load is increased by an elevation in the arterial pressure, the heart, for a few beats, fails to eject as much blood as it had previously. This leaves a residuum in the ventricle which, combined with the

normal return during the next few diastoles again increases the initial length and therefore the energy which can be released by the ventricle during the ensuing systole. As a consequence, the ventricle is then enabled to eject the normal amount against the higher arterial pressure.

EFFECTS OF CHRONICALLY INCREASED DIASTOLIC VENTRICULAR VOLUME

Increase of either venous return or arterial resistance thus leads to dilatation of the ventricles. Such dilatation disappears immediately if the work load is reduced but with persistence of increased work load such as is seen with valvular defects, the dilatation is maintained. After a period of days to weeks, the dilatation leads to hypertrophy (Rather, 1949) of the muscle fiber, thus increasing the work which can be done during a given systole and resulting in return of the initial ventricular volumes toward normal, but of course never completely back to normal. The hypertrophy may eventually disappear if the work load is returned to normal but if the increased work load persists indefinitely, the hypertrophy is likewise maintained. Further augmentation in work load, as by additional damage to the valve, leads again to further dilatation followed by increased hypertrophy. Eventually, however, if the work load is progressively increased, a stage is reached in which the muscle mass has increased out of proportion to the coronary blood supply. Further increase in the work demands of the heart now appears to be limited by the inability of the coronary vessels to supply sufficient blood to meet the increased work demands and leads to onset of chronic failure (Shipley *et al*, 1937).

MYOCARDIAL METABOLISM

In six patients with heart failure resulting from multivalvular heart disease, studied by the technic of coronary sinus catheterization, Goodale and associates (1950) found a decreased oxygen saturation of the coronary venous blood and an increased arteriovenous oxygen difference in concentration which appeared to be correlated with the magnitude of ventricular dilation. The blood flow and oxygen consumption per 100 grams of left ventricle appeared to be within normal limits. They concluded that these patients had no defect in production of aerobic oxidative energy but failure to convert oxidative energy into effective mechanical work.

FUNCTIONAL DISTURBANCES IN ACUTE HEART FAILURE

The phenomena accompanying failure of the heart may be divided into those occurring with acute failure and those with chronic failure. To some extent they are similar and overlap. Acute heart failure, in many respects, resembles traumatic or hemorrhagic hypotension and shock. Acute heart failure may be initiated by phenomena such as sudden onset of extreme tachycardia, myocardial injury due to coronary occlusion, or cardiac tamponade due to rupture or a stab wound of a vessel.

Symptomatology. Symptoms and signs include weakness, faintness, diminished mental alertness, pallor, cold moist skin, feeble, thready, rapid pulse and diminution of blood pressure and, in coronary occlusion, persistent anginal pain. In addition, dyspnea, orthopnea and pulmonary edema may be present and the peripheral veins may be normal, distended or collapsed.

Cardiac Output. Measurements of cardiac output in acute heart failure are not available in any quantity, probably because of the poor condition of the subject. However, the current consensus seems to be that the output is reduced. As a consequence of the reduced stroke volume output by the heart, the pulse pressure becomes narrow and the pulse thready. Th

lowered arterial pressure causes reduced cerebral blood flow, resulting in weakness, faintness and diminished mental awareness

Pulmonary Edema. A large infarct involving principally the left ventricle leads to a sudden reduction of output of the left ventricle with respect to the output of the right ventricle and leads, therefore, to a progressive increase in the pressure in the left atrium and ultimately the pulmonary capillaries, with an increase in the filtration pressure and occurrence of pulmonary edema and of orthopnea. The degree of pulmonary edema probably depends on whether chronic congestive heart failure has been present prior to the onset of the acute coronary occlusion For a further discussion of pulmonary edema in chronic heart failure, see page 238

Venous Pressure. Peripheral venous distention may not be marked in the absence of an increase in blood volume; in fact, the peripheral veins may actually be collapsed, possibly because of the operation of a venous constrictor mechanism responding to the decreased minute volume of circulation (see page 241)

ANALYSIS OF DISTURBANCES IN FUNCTION IN CHRONIC CONGESTIVE HEART FAILURE

Symptomatology. Chronic heart failure may develop as a result of any of the conditions mentioned above under Acute Heart Failure plus, of course, all of the list of causes given in Table IV-2. It is characterized by a gradual onset with repeated attacks of mild heart failure with exertion, gradually progressing to heart failure, even at rest, if the cardiac lesion becomes severe enough. Symptoms and signs which may result from chronic heart failure include dyspnea on exertion and if severe enough, even dyspnea at rest, venous distention, edema, ascites, hydrothorax, enlargement of the liver, cyanosis, pulmonary edema, cough, tachycardia, cardiac enlargement, cachexia and albuminuria.

Cardiac Output. Earlier studies appeared to indicate that cardiac output was within normal limits in heart failure (Harrison, 1939). More recent evidence (Altschule, 1938; Stewart *et al.*, 1940a; Seymour *et al.*, 1942; Merrill, 1946; Suarez *et al.*, 1946; Hickam and Cargill, 1948, Stead *et al.*, 1948, Harvey *et al.*, 1949; Ferrer *et al.*, 1950) demonstrates that, in mild cardiac failure without dyspnea at rest, the cardiac output at rest may be within normal limits but that, with exertion, the cardiac output fails to increase to the extent that it would in normal persons. The more severe the cardiac failure the less is the increase in output with exercise until, with dyspnea, cardiac output is reduced below normal, even at rest (low-output failure). In some instances, heart failure may be present at rest with an output which would be considered normal or even above normal, but almost invariably in these individuals there is an associated anemia or the metabolic rate is elevated above normal; and also in these individuals the output is inadequate to meet the elevated bodily needs (high-output failure; Paine and Smith, 1949, Stead, 1949)

SYSTEMIC BLOOD FLOW

Concurrently with the decrease in cardiac output, systemic blood flow is reduced Arterial pressure, however, is often not decreased. The maintenance of a normal arterial pressure is the result of peripheral systemic vasoconstriction probably induced reflexly.

The vasoconstriction is evident in the skin and kidneys. Cutaneous vasoconstriction may be in part responsible for the slight fever occasionally seen in patients with cardiac failure (see page 246). Vasoconstriction in the kidney is usually quite intense in congestive heart failure and may diminish renal blood flow to as little as one-third of normal (Stead, 1948). However, in acute reduction of cardiac output produced in dogs by constriction of the pul-

monary artery, renal blood flow was reduced less than cardiac output, resistance to flow was augmented only slightly, compared to the total peripheral resistance (Berne and Levy, 1950). The reduced renal flow is probably responsible in part for the retention of salt and water which contributes to the edema in heart failure (see pages 239 and 243).

Cerebral blood flow was found by Scheinberg (1950) to decrease in proportion to the cardiac output in heart failure. Cerebral oxygen consumption was significantly reduced below normal, and the cerebral arterio-venous difference in oxygen concentration and the cerebral vascular resistance to flow both increased. The hepatic (splanchnic) blood flow in 13 patients with cardiac failure was found to be 200 to 800 (average 535) ml per sq M of body surface. In 14 control subjects the hepatic blood flow was 600 to 1160 (average 850) ml per sq. M. of body surface. In the first group the arterial-hepatic vein oxygen difference was 5.5 to 12.8 ml O_2 per 100 ml. of blood whereas in the controls the difference was 3.3 to 5.9 ml O_2 per 100 ml. of blood. The reduction in hepatic flow, in contrast to that in the kidney, was found to be about in proportion to the simultaneous decrease in cardiac output (Myers and Hickam, 1948).

Oxygen Index. Perhaps the most constant finding in all types of heart failure is a disproportion between the cardiac output and the metabolic rate (Briggs *et al.*, 1948), that is, in the ratio of the oxygen supplied by the blood to the tissue per minute to the metabolic rate of oxygen uptake per minute by the tissues. Little (1949) calls this ratio the *oxygen index* (O.I.) It may be expressed mathematically as follows:

$$\text{O.I.} = \frac{\text{O}_2 \text{ supply/sq. M.}}{\text{O}_2 \text{ consumption/sq. M.}}$$

$$= \frac{\text{Arterial O}_2 \text{ (ml./100 ml. blood)}}{\text{A-V O}_2 \text{ difference in ml./100 ml.}}$$

Variations in oxygen index in heart failure. The oxygen index is reduced at rest and very markedly reduced with exertion in many forms of heart failure, particularly congestive heart failure, the degree of reduction depends on the severity of the symptoms associated with the exertion. Hickam and Cargill (1948) have plotted the arteriovenous oxygen difference against the oxygen uptake and find that, in normal persons, large increases in oxygen consumption with exercise are accompanied by only slight elevations in arteriovenous oxygen difference. In other words the cardiac output paralleled the metabolic demands of the tissues. In the patients with congestive heart failure, however, exertion may be accompanied by a very marked increase in the arteriovenous oxygen difference. In such patients the cardiac output has failed to increase in proportion to the oxygen consumption. In patients with mitral stenosis without congestion, Hickam and Cargill found normal cardiac output and arteriovenous differences, however, in these patients also the cardiac output did not increase normally with exercise and, as a result, a much greater increase in arteriovenous difference was seen in these patients than in normal persons (low-output failure).

Brannon and associates (1945) observed that, in subjects who were normal except for anemia, cardiac output did not increase with anemia until the hemoglobin was reduced to around 7 grams per 100 ml.; with hemoglobin below this level, cardiac output at rest progressively increased. In such persons, the cardiac output was increased but the oxygen supplied to the tissues was always proportionately less than the metabolic rate, with the result that the arteriovenous difference was always increased. In these persons, also, as pointed out by Sharpey-Schafer (1945) and McMichael (1947), a still further marked reduction in the ratio of oxygen supply to

oxygen demand was observed with exertion, particularly in the presence of heart failure (high-output failure).

Classification of Severity of Chronic Heart Failure. On the basis of the above discussion, heart failure may be graded as follows

Mild heart failure. At rest, symptoms are absent, cardiac output is normal, and the ratio of tissue oxygen supply to metabolic demand is normal. With moderate exertion, slight dyspnea appears and the oxygen index is slightly below normal. With severe exertion, cardiac output fails to increase in proportion to the exertion, marked dyspnea is present, and there is a considerable increase in arteriovenous oxygen difference and reduction in the oxygen index (Starr, 1939).

Moderate heart failure. No symptoms are noted at rest but the cardiac output is slightly decreased below normal, with a resulting slight increase in arteriovenous oxygen difference and reduction in the oxygen index. With moderate exertion the cardiac output fails to increase adequately, and severe dyspnea, a considerable increase in the arteriovenous oxygen difference, and a marked reduction in the oxygen index occur.

Severe heart failure. At rest the cardiac output and oxygen index may be reduced considerably and the arteriovenous oxygen difference increased. Very little increase in cardiac output occurs with moderate exertion or such exertion may even lead to a reduction in cardiac output and a very marked increase in arteriovenous oxygen difference and reduction in the oxygen index.

Pulmonary Edema. Pulmonary edema may be seen following exercise, with sudden mechanical overload of an impaired left ventricle; in instances of severe mitral stenosis or following sudden reduction of contractile myocardium by myocardial infarction, or coronary insufficiency involving preponderantly the left ventricle; *i.e.*, in any condition in which the left atrial pressure may be abnormally elevated, leading to an elevation in pulmonary capillary pressure. The occurrence of the edema depends, of course, upon a reasonably adequate functioning of the right ventricle which must develop sufficient pressure to raise the pulmonary capillary pressure above the oncotic pressure of the plasma proteins. In patients with moderate chronic heart failure with increase in blood volume and dependent edema, pulmonary edema is especially likely to develop upon retiring and to lead to the phenomenon of nocturnal dyspnea or cardiac asthma. During recumbency, tissue fluid, which was entrapped in the dependent portions while the patient was erect, is mobilized into the blood stream, increasing the systemic central venous pressure and the output of the right ventricle. Failure of the left ventricle to handle the increased load of blood delivered to it by the right ventricle leads to elevation in left atrial and pulmonary capillary pressures and to the development of pulmonary edema. This phenomenon may at times be precipitated by exciting dreams which presumably serve to mobilize extra blood from the blood reservoirs (Perera and Berliner, 1943; Battro *et al.*, 1949; Hilden, 1949)

It is postulated that pulmonary edema may result from reflex pulmonary arteriolar dilatation, resulting in a rise of pulmonary capillary pressure. Such phenomena may be responsible for the pulmonary edema seen in diseases of the central nervous system, such as skull fractures and cerebral hemorrhage (Paine and Smith, 1949). Pulmonary edema may be initiated by pulmonary irritating poisons and by lowering the plasma protein concentration (Paine *et al.*, 1949).

Blood Velocity (Circulation Time). Evidence for the increased pulmonary capillary pressure in instances of mechanical

overload of the left ventricle and in mitral stenosis is found in the decreased velocity of blood flow through the lungs This can be estimated from the arm to tongue circulation time. Since the circulation time is relatively much more prolonged than the cardiac output is reduced one must assume that the vascular system between the arm veins and the tongue including principally the pulmonic capillary bed, is dilated and thereby leads to a more sluggish rate of flow.

Blood Volume. Most authors agree that blood volume is increased in chronic heart failure, particularly in the presence of systemic congestion (Seymour *et al*, 1942, Warren and Stead, 1944; Moore, 1945, Perera, 1945). The increased blood volume closely parallels the increase in total weight of the body and the degree of edema

An increase in the total number of circulating red cells and an increase in the total number of grams of circulating proteins are also seen in heart failure It is not known whether these represent compensatory mechanisms, induced directly by the reduction in cardiac output in heart failure, or whether they represent an attempt by the liver and bone marrow to compensate for the increase in plasma and body fluid volume by an increased production of cells and proteins in an attempt to maintain a normal blood composition. The latter would seem to be the more likely, since in congestive heart failure the concentration of protein and of red cells is less than normal despite the increase in the total quantity of each.

Sodium Chloride and Water Excretion. Recent studies (Warren and Stead, 1944, Merrill, 1946; Burch and Reaser, 1946, Reaser and Burch, 1946, Threefoot *et al*, 1947; Mokotoff *et al.*, 1948; Borst, 1948) in congestive heart failure indicate a reduction in the excretion of salt and water.

It was formerly thought that reduced excretion of water was the primary factor in heart failure This concept is supported by the studies of Miller (1950) who noted that, during relief of cardiac edema, sodium appeared to move into the body cells This would be expected if the primary factor was retention and excretion of water during the development and relief of the edema Most other studies, however, indicate that retention of sodium is the primary factor and that water may be retained secondarily, probably to maintain a normal osmotic pressure of the extracellular fluid. This concept is supported by the following observations (a) Patients with congestive failure may be relieved of their edema without restriction of water intake, provided that either sodium intake is restricted (Schroeder, 1941; Wheeler *et al*, 1947, Scudder *et al*, 1947; Crutchfield and Wood, 1948) or diuretics, such as the mercurials which increase sodium excretion, are administered, (b) if cardiac patients who have just recovered from edema are given sodium chloride, they rapidly reaccumulate edema; on the other hand, if they are given free access to water, edema does not increase and may even be reduced; (c) the effect of the sodium chloride seems to be related to the sodium ion since administration of sodium bicarbonate increases edema, whereas ammonium chloride administration leads to a reduction of edema (Stead, 1948)

The mechanisms by which this reduction in sodium excretion is brought about are still being debated. The consensus is that the rate of glomerular filtration and the renal blood flow are reduced as the cardiac output declines. According to one opinion, these reductions in renal function *per se* are sufficient to explain the diminished sodium and water excretion; another opinion holds that specific antidiuretic mechanisms operate over and above the effects attributable to reduced renal blood flow and glomerular filtratio

Blake and co-workers (1949) compressed the inferior vena cava between the left and right renal veins in anesthetized dogs and found evidence that elevation of venous pressure plays a role in the genesis of cardiac edema.

Hwang and associates (1950) partially compressed the inferior vena cava and noted a temporary reduction in renal blood flow, glomerular filtration and sodium excretion which was proportionate to an elevation in renal venous pressure, however, within a short while all three returned to normal values

Merrill, in 1946, stated that the reduced salt and water excretion are caused by a reduced glomerular filtration due to efferent glomerular arteriolar constriction which parallels the reduction in cardiac output. His conclusion was based on the finding that the amount of sodium chloride reabsorbed was more or less proportional to that filtered through the glomerulus.

Selkurt and co-workers (1949) progressively reduced the pressure in the left renal artery by compression of the aorta between the two renal arteries; the right served as a control. Renal flow (para-aminohippurate clearance) and glomerular filtration (creatinine clearance) were well maintained between pressures of 150 to 100 mm. Hg These two functions decreased progressively below 100 mm Hg, the glomerular filtration declining more rapidly; they ceased at about 60 mm. Hg Sodium excretion decreased rapidly as glomerular filtration fell and ceased when the sodium load presented to the kidney fell below 3 9 millimoles per minute in each kidney. These studies indicate that sodium excretion may be reduced relatively more than cardiac output, renal blood flow or glomerular filtration. They suggest that this phenomenon is the result of inherent activity of the renal tubules and that a specific stimulus to reabsorption of sodium does not have to be supplied to the renal tubules. These authors believe that this excessive tubular reabsorption of sodium when glomerular filtration is low, is directly related to production of edema in chronic congestive heart failure. Selkurt and Post (1950) found, in addition, that reabsorption of sodium was related to the sodium load presented to the tubules when concentration of blood sodium was varied, as the sodium was increased above a threshold amount (millimoles of sodium per minute in each kidney) in the glomerular urine, the amount of sodium in the bladder urine rapidly increased.

The increased reabsorption of sodium does not appear to be related to diminution in any specific tubular function since the maximum tubular capacity for excretion of para-aminohippurate and for reabsorption of glucose are within normal limits (Grossman *et al*, 1950). The reduction in renal blood flow and the renal efferent arteriolar constriction in congestive failure do not appear to be the result of reflexes, they may be initiated by a humoral mechanism (Merrill *et al.*, 1946; Mokotoff and Ross, 1948).

In contrast to the above findings are those of Greve and associates (1951). The latter administered 2 0 mg. of Digitoxin to normal subjects and induced a decrease in cardiac output which was accompanied by a decrease in excretion of creatinine but apparently no change in excretion of sodium.

Burch and Reaser found in their studies on the excretion of radio-sodium in congestive heart failure that 95 to 98 per cent of the filtered sodium instead of the normal 90 to 95 per cent is reabsorbed. They believe that this increased reabsorption is far more important than the reduction in glomerular filtration in explaining the retention of sodium in the body in congestive failure, and that some specific stimulus to the tubules to reabsorb sodium exists. (See also Merrill, 1949.) The source of such hor-

monal or secretory mechanism is not known, although it has been postulated that it may represent an increased output of adrenocortical hormone.

Water is also retained with the sodium, probably in an attempt by the body to maintain osmotic equilibrium rather than a direct effect from the mechanism leading to the sodium reabsorption Increased pitressin secretion by the pituitary may be responsible for the retention of water which accompanies the salt retention An antidiuretic factor has been extracted from the urine of patients with congestive failure; however, it does not have the characteristics of commercial Pitressin (Bercu *et al.*, 1950).

Impairment of liver function may be related to production of edema in chronic congestive failure, which in turn may be the result of inability of the liver to inactivate an antidiuretic factor (Zak, 1949) In line with this hypothesis is the observation that diuretic therapy is more effective in the presence of a normal liver (as determined by biopsy of tissue removed by needle) than when the liver shows evidence of cirrhosis (White *et al*, 1951)

Elevation in Central Venous Pressure. A common accompaniment of cardiac failure is a rise in the central venous pressure and distention of the central systemic veins. Three mechanisms could be responsible: (a) acute failure of the right ventricle to remove blood from the central venous reservoir at the same rate that blood is returning from the periphery. This mechanism would be comparable to that leading to a rise in left atrial and pulmonary capillary pressure seen in acute failure of the left ventricle (Richards *et al.*, 1942); (b) an increase in total blood volume with resulting distention of all the blood vascular system and, since the central venous reservoir is the most distensible, this might be expected to contain the greatest quantity of the added blood volume; and (c) a reduction in vascular capacity (venous constriction). It is probable that all three mechanisms play a part (Landis *et al*, 1946).

Role of Impaired Cardiac Ejection. With exercise the central venous pressure rises slightly in normal persons and markedly in patients with cardiac disease. In both the rise may be due to the increased venous return. However, in patients with cardiac disease, the increased return may cause such an increase in the diastolic volume of the heart that the heart decompensates, with the result that the cardiac output per beat is reduced by the overdistension. This would lead to further retention of blood in the ventricle (Nylin, 1943) and to a rise in the central venous pressure. However, in cardiac patients the rise in central venous pressure is greater than could occur with complete cessation of the normal heart, which would be equivalent to complete heart failure Therefore, some mechanism other than damming back of blood by the failing ventricle must be responsible for the very high central venous pressures seen in chronic heart failure (Starr *et al.*, 1943; Landis *et al*, 1946)

Role of Blood Volume. Starr and Rawson (1940) and Starr (1940) found that venous pressure rises only late in congestive failure after a considerable increase in blood volume has occurred, and that the central venous pressure returns towards normal before the blood volume is restored to normal. They, therefore, believe that the increase in blood volume is the cause of the rise in central venous pressure rather than the reverse as originally proposed by Harrison (1939). This conclusion is supported by the finding that the venous pressure after death in subjects dying of congestive heart failure is much higher than in subjects dying from other causes.

Role of Reduction of Vascular Capacity. McMichael and associates (1943) believe

that in heart failure from anemia the blood volume is below normal and the cardiac output is above normal both at rest and during exertion, but that the central venous pressure, while normal at rest, becomes elevated with failure. This, they state, could be explained only by a reduction in vascular capacity during rest with further reduction during exercise They point out that central venous pressure falls with acute hemorrhage but that venous pressure and cardiac output return towards normal several hours to a day or two after an acute hemorrhage, at which time the blood volume is still below normal. They feel that this is due also to a reduction of vascular capacity, *i e*, venous constriction and that it must depend on some humoral mechanism for its genesis. (See also McMichael, 1949)

Parallelism of venous pressure and venous oxygen tension. Little (1949) made a statistical study of the relationship between the central venous pressure and various other measures of cardiac function. He found that while venous pressure tended to become progressively elevated with increase in blood volume, the correlation was not good. A much better correlation was found between the increase in venous pressure and the venous oxygen partial pressure. He postulates that a reduction in the venous oxygen partial pressure in some way stimulates the mechanism leading to a reduction in vascular capacity which in turn expresses the blood toward the central venous reservoir. He believes that the operation of this mechanism explains, in part at least, the rise in central venous pressure seen in normal persons with exercise and the much greater rise seen in patients with heart failure, since in the latter the venous oxygen partial pressure is reduced much more.

Possible relationship to blood lactic acid. In order to accept the venous oxygen partial pressure as the stimulus for such venous constriction, it will be necessary to find in the systemic venous or the pulmonary arterial circuits, chemoreceptors capable of sensing the venous oxygen partial pressure. Since no such mechanism has as yet been described, it seems possible that the stimulus to reduction of vascular capacity might arise from the chemoreceptors known to exist in the systemic arterial circuit. In severe exertion or in other conditions in which the oxygen supply to the tissues is reduced below normal, *i e*, in which the arteriovenous oxygen difference is increased or the venous oxygen partial pressure reduced, lactic acid and other abnormal products of metabolism are produced Since these products are not removed by the lungs, it might be anticipated that they could be carried to the systemic arterial circuit where they could excite appropriate chemoreceptors in the aortic and carotid bodies. Supporting this point of view is the prolongation of the rise in venous pressure and cardiac output seen during the period of oxygen debt following exertion, during which it has been shown that lactic acid remains elevated in the circulation.

Arterial and venous constrictor mechanisms Discharge of impulses from the chemoreceptors will induce increased sympathetic nerve discharges from the medullary centers. This will cause widespread increase in peripheral resistance by causing arteriolar and terminal arterial vasoconstriction This must be the mechanism for maintaining the arterial pressure at normal levels despite the decreased cardiac output (Stewart *et al.*, 1946). This mechanism is possibly overactive during heart failure since the mean arterial pressure of many patients declines as compensation returns. Such sympathetic activity could also serve to reduce the capacity of the vascular bed by causing afferent arteriolar constriction and efferent venular dilatation in the spleen, liver and

intestines and generalized constriction of the larger veins. The increased sympathetic nerve activity could also serve to increase the contractile power of the heart and thus to increase the cardiac output at least in normal subjects. An example of the operation of such a mechanism is the response to intravenously injected epinephrine. It not only increases the arterial pressure, but also causes a rise in central venous pressure, a reduction in splenic volume and an increase in cardiac output. It is also possible that, to some extent, the increased cardiac contractility might be produced by the direct effect of metabolic products in the blood, particularly lactic acid, acting upon the myocardium.

Systemic Edema. The increase in tissue fluid and the systemic edema of congestive failure were formerly attributed primarily to the elevation of central venous pressure and to a reduction in total plasma proteins and tissue tension. It apparently was not appreciated that in congestive heart failure the total circulating proteins are increased despite the reduction in protein concentration. If one computes the actual elevation in venous pressure in the dependent part of the body caused by the rise in central venous pressure, it will be found that the increase in total hydrostatic pressure, even in severe congestive failure, is not large because the central venous pressure is rarely elevated more than 10 to 15 cm. of water, whereas in the normal person, standing quietly, the pressure in the veins in the feet is of the order of 100 cm. of water. In other words, the pressure in the feet would be increased only 10 per cent.

More important in the development of edema is the retention of sodium and water by the kidney. (See page 239.) This will serve to elevate blood volume and capillary pressure and to reduce the effective oncotic pressure of the plasma proteins to the point where filtration of water and dissolved substances into the tissues must occur, thus leading to edema. The edema of congestive failure does not result from increased capillary permeability to protein (Stead and Warren, 1944). (See page 239.) Care must be taken in the administration of mercurial diuretics when sodium intake is restricted, or hyponatremia may result. Occasionally severe lowering of the plasma sodium may cause anorexia, apathy, nausea, muscular pains, psychosis and coma, and may be accompanied by oliguria and azotemia (Citron *et al.*, 1951).

Relief of edema by administration of digitalis probably depends upon the improvement in cardiac output which is brought about by the drug. The improved cardiac output apparently abolishes the stimulus to the kidney to retain salt and water (Dock, 1949). Relief of edema by mercurial diuretics is probably brought about primarily by diuresis of sodium by decreasing the resorption of sodium by the renal tubules, *i.e.*, the lowered plasma osmotic pressure caused by the diuresis of sodium is probably responsible for the inhibition of pitressin output by the pituitary gland and consequently for secondary diuresis of water.

Pleural effusion is a frequent finding in chronic congestive failure. In one series of 42 patients the effusion was on the right side in 28 and was bilateral in one. The exact mechanism of production of the effusion is not known. Both increased intracapillary pressure and increased capillary permeability are involved (Tinney and Olsen, 1945).

Hepatic congestion. Swelling and tenderness of the liver are seen frequently with heart failure. Most of the cellular damage and congestion is in the region of the central veins. The changes have been ascribed to the mechanical effect of the elevated systemic venous pressure. However the pressure in the periphery of the lobules, where the blood from the por-

tal vein enters the hepatic capillaries must be higher than that in the capillaries near the central veins of the lobules from which the blood leaves the lobule to enter the hepatic vein. Such damage, on the other hand, could result from hypoxia due to decreased blood flow, the hepatic cells in the periphery of the lobules, being the first to receive the portal venous blood, would be better oxygenated than the hepatic cells located in the center of the lobules The occurrence of similar lesions in the liver in anemia favors this latter concept. Liver function may be disturbed in heart failure. Serum bilirubin is frequently elevated, and there may be retention of bromsulfalein (Paine and Smith, 1949).

Hyperpnea, Dyspnea and Orthopnea. Hyperpnea is a clinical *sign* and may be defined as increased minute volume of breathing, the rate or depth of breathing or both being augmented. Dyspnea is a clinical *symptom*, noted by the patient, of difficult or labored breathing or of unsatisfied desire for air While the two frequently occur together there is no close parallelism in their intensity, and moderate hyperpnea may occur in the normal person without dyspnea

Chemical Factors Contributing to Hyperpnea. *Hypercapnia* Although the function of respiration would seem to be proper oxygenation of arterial blood, ordinarily the medullary respiratory center is actually principally concerned with regulation of arterial blood pH through its control of elimination of carbonic acid. A very slight increase in arterial pCO_2* of + 1.5 mm. Hg (normal 40 mm. Hg) or decrease in pH, by the effect on the medullary center, results in doubling of the respiratory minute volume. Respiration is slowed in a similar manner by reduction of pCO_2. With excessive elevation of arterial pCO_2, additional reflex stimulation of the medullary respiratory center occurs through impulses generated in the carotid and aortic body chemoreceptors and transmitted to the medullary centers *via* the ninth and tenth cranial nerves.

Hypoxia. An increase in pO_2 above normal has no effect on the respiratory minute volume; and a considerable decrease in arterial pO_2 (from 100 to 70 mm. Hg) is necessary to double the respiratory minute volume, through its influence on the carotid and aortic bodies. The relatively high percentage of oxygen in the inspired air (20.9 per cent) compared with the lower percentage of CO_2 in the alveolar air (5.5 per cent) assures a sufficient respiratory exchange which will eliminate the proper volume of CO_2 and cause an intake of a slightly larger volume of oxygen than is required under normal circumstances (respiratory quotient = volume of CO_2 eliminated/volume of O_2 consumed = 0.8).

Lactic acid and other metabolites. Lactic acid and possibly other products accumulate in the blood whenever tissue oxygenation is incomplete, and serve as potent stimulants to respiration. Lactic acid may affect both the medullary centers and the carotid and aortic body chemoreceptors; the former are probably the more sensitive.

Other sensory receptors. Chemoreceptors, supposedly sensitive to the effects of asphyxia (reduced O_2, increased CO_2) are said to be present in the pulmonary artery, lungs and abdominal viscera Afferent impulses from active skeletal muscles are also said to assist in the production of the hyperpnea of exercise but the nature of the stimulus to the sensory endings has not been clarified (Harrison *et al*, 1932). Elevation and depression of arterial pres-

* pCO_2 is the "partial" pressure of the CO_2, *i e*, the pressure which it is constantly exerting to escape from solution or to diffuse through membranes The term pO_2 used below refers similarly to the "partial" gas pressure exerted The term "partial" refers to that part of the total gas pressure which is exerted by the indicated gas

sure produce momentary decreases and increases in respiration through their effects on the aortic and carotid sinus pressoreceptors.

Relationship of Heart Failure to Hyperpnea. *Reduced minute volume of circulation.* Reduction of the minute volume of circulation will decrease the delivery of oxygen to the tissues, increase the oxygen utilization (ml. of oxygen removed per 100 ml. of blood flowing through the tissues) and lower the average tissue capillary oxygen tension. At a critical level lactic acid will be produced which will serve to stimulate respiration, probably simultaneously with activation of the arterial and venous constrictor mechanisms (see page 242). Under such circumstances, arterial pO_2 will be normal and the pCO_2 may be reduced below normal

Pulmonary congestion and edema Exchange of pulmonary oxygen and carbon dioxide is reduced in the presence of relative failure of the left ventricle by the thickening of alveolar walls and alveolar accumulation of fluid As a consequence, arterial pO_2 declines and pCO_2 rises. These changes, added to the accumulation of lactic acid noted above, provide further stimulus to hyperpnea during episodes of heart failure.

Dyspnea. Since dyspnea is a sensation, its elucidation is limited to studies on man Wiggers (1949) has proposed that dyspnea be considered to be present when the expiratory muscles are brought into play, but, in the absence of an adequate statistical comparison of the severity of symptoms with the degree of use of the expiratory muscles, it is probably better to continue to define dyspnea as given above The term "active expiration" might be more suitable for the sign defined by Wiggers as dyspnea.

A form of dyspnea, characterized by shortness of breath or air hunger, is probably caused by failure of the cardio-respiratory machinery to prevent undue changes in arterial pO_2, pCO_2, or lactic acid concentration Actual labored or difficult breathing, which is sometimes characterized as a sense of constriction of the chest, occurs in asthma and emphysema and is probably related to mechanical difficulty in movement of the tidal air. Similar difficulty may be experienced with excessive elevation of the diaphragm by abdominal distention and with the impaired elasticity of the congested lung in heart failure. Abnormal sensitivity to the Hering-Breuer afferent impulses normally generated in the lung during expansion and collapse may be responsible for the sensation, complained of by some psychoneurotic patients, that they "need to but can't take a deep breath." It is suggested by some authors that, in a similar manner, an exaggerated discharge of these impulses from the congested and more rigid lungs augments the dyspnea during episodes of congestive heart failure

Orthopnea. Patients with moderate to severe cardiac disease, especially with failure at rest, experience less dyspnea when sitting up leaning over a bed table or when in a semi-reclining position than when they are in a horizontal position. The degree of such orthopnea is often expressed in terms of the number of pillows required by the patient The exact mechanism by which elevation of the cephalad part of the body reduces dyspnea is not known. In the horizontal position such patients have an arterial blood oxygen tension that is lower than normal. Factors that contribute to this condition are impaired mechanical respiration resulting from undue elevation of the diaphragm, increased rigidity of the lungs and lessened negativity of the intrapleural pressure caused by the pulmonary congestion, and impaired gaseous exchange resulting from increased pulmonary

edema The latter are probably caused by the elevated pressures in the right atrium and pulmonary trunk. In the normal patient, recumbency is accompanied by an increased cardiac output which is considered to be due to elevation of right atrial pressure by mobilization of fluid from the previously dependent parts of the body. Failure of this increased output to occur in cardiac patients, especially if due to inability of the left ventricle to handle the increased venous return, would be a primary cause of increased pulmonary congestion and edema when recumbent

Lessening of dyspnea by elevation of the head without raising the chest, has been described, but I have rarely been able to demonstrate this phenomenon. It has been ascribed to lowering of the cerebrospinal fluid pressure and to decreasing the pressure in the cerebral veins (Altschule *et al*, 1945). Since cerebral arterial pressure would be lowered as much or more than the cerebrospinal fluid or venous pressures by elevation of the head, any beneficial effect on cerebral blood flow that might occur could not be ascribed to an increase in the difference in hydrostatic pressure between the cerebral arteries and veins

Fever. Moderate elevation of body temperature, in proportion to the degree of congestive failure, has been reported. In these patients the fever could not be attributed to infection (Cohn and Steele, 1934). In patients with congestive failure such fever was associated with subnormal cutaneous temperatures whereas in infections, fever is associated with cutaneous temperatures which are above normal (Steele, 1934). The fever in congestive failure may be attributed to impaired transport of heat to the body surface owing to (1) decreased cardiac output relative to heat production, and (2) cutaneous vasoconstriction (Altschule, 1949). However, it should be remembered that an elevation of body temperature may induce heart failure, especially if it occurs as a result of a hot, humid environment which makes it impossible for the patient adequately to eliminate heat. Such patients may suffer from dyspnea and apprehension (Burch, 1946).

Heart Strain. The term heart strain appears to have been used by various authors with a variety of meanings. By some, at least, it has been used to imply an acute distress, equivalent possibly, to the type of "strain" which could produce acute ventricular dilation. The records published by most investigators (Burch and Winsor, 1945; Katz, 1946; Wiggers, 1949) appear on the other hand to correspond more closely to those noted in authenticated cases of ventricular hypertrophy without acute dilation (Myers, 1950a, b). It would seem better to eliminate the term heart strain and refer to axis deviation or to heart position, to ventricular hypertrophy, or to acute ventricular dilation (associated in many cases with some relative ischemia of the dilated ventricle).

Ventricular Hypertrophy. Ventricular hypertrophy occurs as a physiologic response to any condition which produces ventricular dilation. In the absence of coronary artery disease such dilation results from any factor that increases the work load on the heart. Conditions such as aortic valvular stenosis or insufficiency and systemic arterial hypertension commonly lead to predominant left ventricular hypertrophy while abnormalities such as mitral stenosis, and pulmonary arteriolar sclerosis lead to predominantly right ventricular hypertrophy (see page 233).

Acute Ventricular Dilation. Acute dilation of a ventricular chamber presumably may occur whenever the heart goes rapidly into failure, due to a mechanical overload. Such dilation may occur in either chamber. It is likely to be superimposed upon a chamber already atrophied by an increased

work load, occasioned by the same factors which ultimately lead to the acute failure The acute dilation will be associated with an elevated myocardial metabolic demand, which the coronary vessels may not be able to meet.

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Congenital Malformations of the Heart and Great Vessels

A. Malformations of the Atrial Septal Complex

JESSE E. EDWARDS

DEFECTS OF THE ATRIAL SEPTUM

Defects Involving Region of Foramen Ovale

A DEFECT of the atrial septum may take one of several forms based on location: It may involve the region of the foramen ovale, it may lie in the inferior portion of the atrial septum, it may be in areas removed from the first two locations, or it may involve the entire atrial septum

Probe-Patency of the Foramen Ovale. *In about 20 to 25 per cent of normal adult* human hearts, though no functional interatrial communication exists, it is possible to pass a probe from the right atrium into the left (Scammon and Norris, 1918; Patten, 1938; Wright, Anson and Cleveland, 1948). The probe passes from right to left obliquely upward from the fossa ovalis to and beside the valve of the foramen ovale (Figures II-19 and II-43). This condition, in which the foramen ovale is functionally closed by a competent valve which prevents return flow from left to right atrium, has been termed by Patten (1931) *probe-patency of the foramen ovale.* That probe-patency should be considered a variant of the normal is logical both in view of the frequency of the condition and because, unless the postnatal atrial pressure relations are abnormal, no blood will pass through the vestigial channel. Under conditions of normal cardiovascular function *the pressure in the left atrium exceeds that* within the right. The valve of the foramen ovale is thus pressed against the rest of the atrial septum and no shunting of blood between the atria occurs. Under conditions of abnormal function when the pressure in the right atrium exceeds that in the left atrium, it is possible for blood to flow from the right atrium into the left atrium, as it did in the fetus

A striking example of such an oc

rence is sometimes encountered in cases of pulmonary embolism when the increased resistance to pulmonary flow is reflected in an increased pressure within the right ventricle and then in the right atrium. When this occurs in the presence of probe-patency, blood will flow across the atrial septum from the right, into the left atrium (Gross, 1934). If the blood entering the right atrium from the great veins contains more emboli, some of these may pass into the left atrium by way of the incompletely closed channel at the foramen ovale. In this way it is possible for peripheral arterial occlusions to be caused by emboli originating in the right atrium or one of its tributary veins. Passage of emboli across the atrial septum is termed "paradoxic embolism." This condition will be considered at greater length in a later section.

True Patency of the Foramen Ovale. Actual anatomic defects in the region of the foramen ovale may be said to result, in one way or another, from *incompetency of the valve of the foramen ovale* (Figure II-44). A common cause of this condition is an unusually short valve of the foramen ovale. The developmental basis for this condition is clearly evident when one reviews the embryology of the atrial septum.

In Chapter II on cardiac development it was explained that it is normal for a secondary opening (foramen secundum) to develop in interatrial septum primum. Normally this opening remains so small that the persistent part of the septum primum is ample to act as a valve, closing the foramen ovale of septum secundum (Figure II-41). If the process of regression of septum primum is excessive, the valve of the foramen becomes incompetent. In extreme cases the regression may go so far that the valve is almost, or completely, destroyed. In such cases the foramen ovale is left unguarded and an anatomic defect exists which is of functional significance (Figure V-1).



Figure V-1. *a* Atrial septal defect in a woman aged 51 years. The defect, viewed from the left, is on the basis of a short valve of the foramen ovale. Because of the small size of the defect it was of no functional consequence to the patient.

b Atrial septal defect viewed from the left. The valve of the foramen ovale is unusually short, allowing an interatrial communication of significant size. From a young woman who died of a cerebral abscess. (Case 5, from Gates, E. M., Rogers, H. M., and Edwards, J. E. *Proc. Staff Meet., Mayo Clin.*, 22:401-412, 1947.)

A second way in which the foramen ovale may be left inadequately guarded by a valve is represented by defective formation of septum secundum. Septum secundum is normally not a complete partition, having within it an opening called the *foramen ovale.* If, by reason of incomplete growth of septum secundum, the

size of the foramen ovale remains excessively large, its valve, though of normal extent, may still be insufficient to guard the foramen ovale properly.

In examining adult hearts with defects at the foramen ovale it may be difficult to distinguish between these two possible underlying causes of true patency of the foramen ovale As a result of the shunt permitted by such defects, the atria become dilated and so stretch the atrial septum, thus accentuating the disproportion between the size of the foramen ovale and the valve which should guard it.

A third way in which anatomic patency of the foramen ovale develops is represented by regression of septum primum in abnormal locations. It will be recalled that foramen secundum is formed by a cluster of perforations which develop cephalically in septum primum near the superior atrial wall. Eventually these small openings coalesce to form one large one, the foramen secundum Normally that part of septum primum caudad to foramen secundum remains intact and acts as the valve of the foramen ovale (Figure II-41). Occasionally perforations develop caudad to the region where foramen secundum normally forms. If these ectopic perforations in septum primum overlie the foramen ovale in septum secundum, the valve of the foramen ovale is fenestrated and is, of course, incompetent (Figure V-2).



Figure V-2. Atrial septal defect viewed from the left. The defect results from a combination of shortness and perforation of the valve of the foramen ovale. From a woman 37 years of age

In summary, functional defects in the region of the foramen ovale may result from (1) an unusually short valve of the foramen ovale, (2) an unusually large foramen ovale, (3) fenestrations in the valve of the foramen ovale, or (4) any combination of the foregoing. It is of interest from the developmental standpoint that ectopic perforations of the septum primum are not uncommon. These usually overlie intact portions of septum secundum so that no patency of the atrial septum is produced.

Defects Involving Caudal Portion of Atrial Septum

Defects involving the lower portion of the atrial septum are decidedly less common than are defects of the atrial septum involving the region of the foramen ovale When defects occur in the lower portion of the atrial septum the region of the foramen ovale is usually normally formed. In rare instances, however, the two types of defects may be associated. In the chapter on cardiac development it was brought out that the completion of the atrial septum is a relatively complicated matter, in that the process depends upon the fusion of the lower margin of septum primum with the dorsal and ventral atrioventricular endocardial cushions after the latter have fused with each other to accomplish the division of the once-common atrioventricular canal into mitral and tricuspid orifices (Figures II-16 to 18). Fusion of the two atrioventricular endocardial cushions with each other on the one hand,

and with septum primum on the other seems in large measure to be a responsibility of the endocardial cushions. The reason for this view is that whenever defects of the lower part of the atrial septum occur it is common for abnormalities in the atrioventricular valves to exist. These defects will be described in a subsequent section on valvular malformations (page 369). Suffice it to say at this point that defects in the caudal part of the atrial septum usually possess a crescentic superior margin and extend thence toward a point immediately superior to the midpoint of the atrioventricular canal. The functional alterations caused by a defect in the caudal part of the atrial septum *per se* are not different from those caused by defects in the region of the foramen ovale. Since, however, the defects of the caudal part of the atrial septum are often associated with valvular malformations, the latter may create abnormalities not present in hearts with defects at the foramen ovale. These will be described in the appropriate section.

Atrial Septal Defects in Unusual Locations

Defects localized in the cephalic part of the atrial septum are extremely unusual Hepburn in 1887 described one in an adult. This was located cephalic and ventral to the fossa ovalis. In that case there were also anomalous drainage of the right superior pulmonary vein into the superior vena cava and a persistent left superior vena cava. Hepburn related that only one other such instance of septal defect had been described, namely, a case mentioned by Peacock in 1878. In that case the defect was cephalic to the fossa ovalis and distinct from it. The patient was a girl who died of cardiac failure at the age of ten years. The case of Moureyre (quoted by McGinn and White, 1933) showed a small defect ventral to a widely patent foramen ovale. In the specimen described by Wagstaffe (1868) the foramen ovale was closed but an atrial septal defect existed caudal to the entrance of the superior vena cava.

Defects Involving Entire Atrial Septum (Single Atrium)

Less common than defects involving either the region of the foramen ovale or the caudal part of the atrial septum is the condition in which the atrial septum is either completely defective or so vestigial as to constitute, for practical purposes, absence of the atrial septum Though the atrium is single, there are two auricular appendages (Young and Robinson, 1907-08) Among cases of single atrium it is necessary to distinguish those cases in which the ventricular septum is present from those in which it is absent. The former condition is termed *cor triloculare biventriculare*, the latter, *cor biloculare.*

Cor Triloculare Biventriculare. When the ventricular septum is intact, the absence of the atrial septum causes a functional derangement which is essentially like that in cases with large atrial septal defects. There is free mixing of venous and oxygenated blood in the atrium. The predominant direction of flow of blood is toward the right through the tricuspid valve. It is significant that in this malformation the normal differential of pressure between the two ventricles is maintained. This is in contrast to the condition in which the ventricular septum also is absent (cor biloculare).

Though there are usually separate mitral and tricuspid orifices in cor triloculare biventriculare, in the case reported by Cunningham (1948), there was a common atrioventricular valve.

Cor Biloculare. When both the atrial and ventricular septa are absent, the chief matter of consequence is that there are no differential ventricular pressures. The ejectile force is the same, as is the source

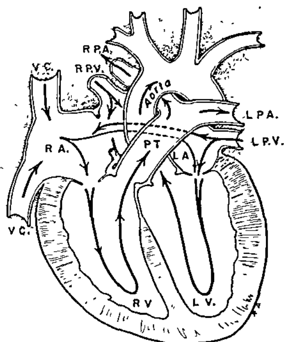


Figure V-3 Plan of the intracardiac circulation in cases of atrial septal defect The predominant interatrial flow is from the left atrium into the right atrium, but a minor degree of flow from the right to the left occurs in some cases *L A*, left atrium, *L P A*, left pulmonary artery, *L P V*, left pulmonary vein, *L V*, left ventricle, *P T*, pulmonary trunk, *R A*, right atrium, *R P A*, right pulmonary artery, *R P.V*, right pulmonary vein, *R V*, right ventricle, *V C*, vena cava

of blood flowing both to the pulmonary and to the systemic circulations. In this important matter cor biloculare is identical with instances in which there is an atrial septum but no ventricular septum, *i e., cor triloculare biatriatum.* The latter condition will be discussed in the section on malformations of the ventricular septal complex. Further discussion of cor biloculare will likewise be found in that section (page 301).

Functional Disturbances and Complications of Atrial Septal Defect

Regardless of the anatomic type of atrial septal defect, the direction of the shunt across the defect is, as a rule, predominantly from the left atrium into the right atrium (Hull, 1949). The volume of this flow varies considerably from case to case.

Among seven living patients who had atrial septal defect studied by Taylor and his associates (1948) by means of cardiac catheterization, the left to right shunt varied from 1.4 to 16.6 liters per minute, five of the patients exhibiting a shunt measuring 7.0 liters per minute or more.

While the predominant direction of flow is from the left atrium to the right atrium, at the same time some venous blood often flows from the right atrium across the septal defect into the left atrium (Figure V-3). This probably results from a combination of eddying of blood near the septal defect and the close association of the entrance of the inferior vena cava and the septal defect (Figure V-4). In cases in which compensation of the right ventricle is maintained, the right-to-left shunt rarely, if ever, reaches sufficient proportions to cause cyanosis.

In the series of Taylor and his associates the lowest oxygen saturation in blood taken from a radial artery was 91 per cent of normal.

During a given period about twice as

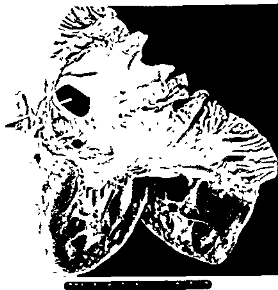


Figure V-4. Atrial septal defect viewed from the right. The proximity of the right atrial entrance of the inferior vena cava to the atrial septal defect probably explains the shunting of some venous blood into the left atrium in this anomaly. From a woman 64 years of age (From Barger and associates, 1948.)







Figure V-5 *a* Exterior of the heart in a man 70 years of age with a large atrial septal defect The enlargement of the right atrium and ventricle and the wide pulmonary trunk are shown
b and *c* The right side of the heart and the left ventricle of a woman aged 24 years who died suddenly with an atrial septal defect
b The right ventricle is dilated and hypertrophied
c The left ventricle is of normal size (From Edwards, J E *Postgrad Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

much blood passes through the right ventricle as passes through the left (Brannon, Weens and Warren, 1945) As a consequence of the added load upon the right side of the heart there is dilatation of the right atrium and right ventricle (Figure V-5*a*), and the right ventricular wall is hypertrophic (Figures V-5*b* and *c*). The right ventricular hypertrophy is the anatomic counterpart of the usual finding of the right axis deviation on electrocardiographic examination. The left ventricle is usually normal in size. The increase in cardiac weight in atrial septal defect i



Figure V-6 *a* Dilated pulmonary trunk in a case of atrial septal defect From a woman 37 years of age The defect in the atrial septum is illustrated in Figure V-2

b. Roentgenogram of the thorax from the case of atrial septal defect illustrated in Figures V-2 and 6*a*. Dilatation of the pulmonary "conus"

predominantly the result of right ventricular hypertrophy

In an analysis of the weights of the hearts in 19 cases of atrial septal defect in which the patients were 14 years of age or older, Roesler (1934) found the average weight to be 574 Gm., the extremes being 1035 and 250 Gm. This average compares closely with the findings of Cosby and Griffith (1949), who observed that in 19 hearts with atrial septal defect the average weight was 592 2 Gm.

As a consequence of the great flow through the pulmonary arterial system the pulmonary trunk and its branches are dilated (Figure V-6*a*). Associated with this change is a relatively narrow aorta. In writings of the earlier authors it was claimed that the disproportion between the size of the pulmonary trunk and the aorta was a manifestation of an additional malformation. This seems an incorrect explanation when one recalls that in these cases the pulmonary blood flow far exceeds the systemic flow. The anatomic changes in the great arteries reflect the relative load, from the point of view of blood volume, placed upon these two great vessels. Roentgenographically the dilated pulmonary trunk is recognized as a prominence in the shadow of the "pulmonary conus," and the excessive pulmonary blood flow by the evidence of congestion of the pulmonary tissues (Figure V-6*b*). Roentgenoscopically there may also be noticed unusual pulsations of the hilar vessels, the so-called "hilar dance." A causal relationship seems to exist between the frequent precordial bulging in patients with atrial septal defect and dilatation of the pulmonary trunk. Very likely the pulmonary arterial dilatation during the period of skeletal development has an influence in molding the shape of the thoracic cage.

Hoarseness in patients with atrial septal defect has been attributed by Erlanger and Levine (1943) to pressure on the left recurrent laryngeal nerve as it lies between the aorta and the dilated pulmonary arterial vessels In two patients, both adult women, they observed paralysis of the left vocal cord. Burrett and White (1945) reported hoarseness secondary to paralysis of the left vocal cord in a woman 43 years of age who had an atrial septal defect. In the case of Wahl and Gard (1931)

hoarseness was evidently secondary to compression of the left recurrent laryngeal nerve by a saccular aneurysm of the left pulmonary artery. Their patient was a girl, aged 19 years, who had an atrial septal defect and, in addition, a cylindrical dilatation of the right pulmonary artery

Patients with atrial septal defect usually bear the defect well for many years, though cardiac failure may result during childhood (Amberg and Willius, 1926)

The patient of Tarnower and Woodruff (1936) lived to the age of 77 years Cosby and Griffith (1949) reported on one patient with atrial septal defect who lived to 78 years and on another who lived to 80 years. In some cases the defect is discovered incidentally, only after death from unrelated causes. Most patients ultimately do show deleterious effects as a result of the malformation. The chief cause of death is failure of the right side of the heart, though this often does not become manifest until the fourth or fifth decade

In the 19 cases with necropsy which Cosby and Griffith studied, the average age at the time of death was 49 years Roesler (1934) found that, if he excluded from his calculations persons dying of unrelated conditions, the average age at death of patients with atrial septal defect was 36 years. He tabulated the age at death in the 62 cases which he reviewed This included patients dying of the defect or from unrelated causes. Table V-1 is taken from Roesler Rarely, sudden unexplained death occurs. In other cases, paradoxic embolism (see later section) is a complication of atrial septal defect, and in still others, cerebral abscess develops without any associated inflammatory disease of the heart (Dry, 1948).

TABLE V-1
Frequency of Atrial Septal Defect, According to Age at Death *

Age in Years	Cases	Per Cent
0-10	5	8 0
11-20	8	12 9
21-30	15	24 2
31-40	9	14 5
41-50	10	16 1
51-60	10	16 1
61-70	3	4 8
71-75	2	3 3

* From Roesler (1934), by courtesy of the author, and the editor of *Archives of Internal Medicine.*

Bacterial endocarditis is a rare complication of those atrial septal defects which are characterized by patency of the foramen ovale. In a study including 45 cases of atrial septal defect in each of which the patient was more than two years of age, Gelfman and Levine (1942) found no instance of bacterial endocarditis. Jacobius and Moore in 1938 mentioned a case of patent foramen ovale in which lesions of subacute bacterial endocarditis were present on the limbus of the fossa ovalis and on the mitral valve No details relative to the age of the patient or the size of the atrial septal defect were given. In an analysis of 19 cases of fatal atrial septal defect, Cosby and Griffith reported one case of bacterial endocarditis. Though the exact site of the infection was not given, the authors stated that the infection did not involve the margins of the defect In the case of Kurz and Fischer (1949) there was involvement of the mitral valve by the lesions of subacute bacterial endocarditis In one of the cases of Bedford, Papp and Parkinson (1941) there was bacterial endocarditis upon the wall of the left atrium. This did not involve the mitral valve nor presumably the margins of the atrial septal defect.

In the case of Geiger and Anderson (1947) the patient was a woman, aged 55 years, who had an atrial septal defect measuring 3 0 cm. in diameter. The mitral valve showed thickening and rolling of the free edges of the leaflets, and the chordae tendineae were thickened and fused There was bacterial endocarditis caused by pneumococcus, type V, involving the anterior leaflet of the mitral valve. The margins of the septal defect were n

involved by the infectious process. In addition to splenic infarcts there were pulmonary infarcts. The latter lesions suggested that vegetations on the mitral valve had broken off and, in the presence of mitral insufficiency, had been carried into the left atrial chamber during ventricular systole. Then the emboli crossed into the right side of the heart and were carried to the lungs. If this interpretation is correct, this case is an example of an unusual form of paradoxic embolism in that the direction of the embolization was from left to right, the reverse direction from that usually taken in paradoxic embolism.

Though rare even in defects of the lower part of the atrial septum, bacterial endocarditis is much more likely to occur with this malformation than in atrial septal defect at the foramen ovale.

Among 56 cases of atrial septal defect involving the lower part of the atrial septum associated with atrioventricular valvular malformations, Rogers and I (1948) found three cases of bacterial endocarditis involving the margins of the defect, the neighboring valves or both. Perhaps the infrequency of this complication in such cases is explained by the fact that many of the patients with defects of the lower part of the atrial septum and associated valvular malformations die at early ages, consequently, the chance of bacteremia which would cause such an infection is relatively small.

A case of Tinney and Barnes (1942) is often quoted as an example of subacute bacterial endocarditis complicating Lutembacher's syndrome. In a restudy of the specimen of the heart in this case Rogers and I offered the opinion that the malformation was not an atrial septal defect in the form of a patent foramen ovale associated with mitral stenosis. We believe that the defect was in the caudal part of the atrial septum, representing a persistence of interatrial foramen primum, and that the abnormality of the mitral valve was a congenital malformation. The bacterial endocarditis involved the margins of the defect and the adjacent mitral valve.

The major pulmonary arteries, in addition to dilatation, may show aneurysmal formation. Foci of atheromatous changes may occur and in unusual circumstances there may be thrombosis upon atheromatous foci (Taussig, Harvey and Follis, 1938).

Okkels and Therkelsen (1932) described an atrial septal defect in a man, aged 31 years. In this patient the pulmonary trunk was the seat of severe atheromatous change. Immediately superior to the valve the pulmonary trunk showed a saccular aneurysm. The latter was filled with a thrombus which extended into and occluded the lumen of the left pulmonary artery. Mention has already been made of the case of Wahl and Gard (1931) in which atrial septal defect was associated with extreme dilatation of the pulmonary trunk and its major branches. The left pulmonary artery was the seat of a saccular aneurysm which was clinically interpreted as a mediastinal tumor. The right pulmonary artery was cylindrically dilated. The patient of Ravault and associates (1947) had atheromas of the pulmonary arterial system. In 1947 Deterling and Clagett reviewed the literature on aneurysm of the pulmonary artery. They indicated that this condition is usually caused either by syphilis of the artery or by the effects of an arteriovenous shunt. In the latter category patent ductus arteriosus is the most common underlying malformation. Atrial septal defect is a relatively uncommon cause of pulmonary arterial aneurysm.

Occlusive lesions of the smaller pulmonary arteries and arterioles are infrequent in cases of atrial septal defect (Welch and Kinney, 1948; Parker and Weiss, 1936). Massee (1947) reported the occurrence in a man, aged 37 years, of atrial septal de-

fect and occlusive lesions in the smaller pulmonary vessels. He described the vessels as "sclerotic, thickened, and markedly dilated." The report of Barger and associates (1948) concerns a woman, aged 62 years, with atrial septal defect and with occlusive lesions in the pulmonary arterioles caused by a metastatic carcinoma secondary to a primary carcinoma of an ovary. This patient's terminal cardiac embarrassment seemed to be related to the occlusive lesions which were interpreted as causing increased resistance to pulmonary blood flow. From this followed a right-to-left shunt with clinical cyanosis This latter case seems to be correctly interpreted as showing the clinical manifestation of *cyanose tardive* which Bard and Curtillet (1889), Abbott (1915) and others have stressed as appearing late in the course of atrial septal defect In the majority of cases of atrial septal defect, however, the appearance of a predominant right-to-left shunt is incident merely to right ventricular failure, the latter resulting from the effects of the load upon the right ventricle caused by the left-to-right shunt.



Figure V-7 Lutembacher's syndrome in a man 51 years of age The heart is viewed from the left showing the large atrial septal defect and the rheumatic mitral stenosis (From Edwards, J E *Postgrad Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

Lutembacher's Syndrome. The combination of atrial septal defect and mitral stenosis usually carries the designation, Lutembacher's syndrome (Figure V-7) This syndrome may be considered a complication of atrial septal defect. In 1933 McGinn and White made a comprehensive review of the literature and reported a new case. According to these authors, the first reported example of the condition which now goes by the name of "Lutembacher's syndrome" was the case of Martineau reported in 1865 Following this report this complex was described by other authors Abbott's case of this condition was described in 1915 while Lutembacher's original report was made in 1916 Lutembacher made a lengthy review of the subject and discussed the variety of viewpoints held as to the cause of the condition, he also discussed the hemodynamics of the condition

Including the case of McGinn and White (1933), the report of these authors contained an analysis of data on 24 cases. They stated that there is a distinct predilection for the female sex The report of Gibson and Roos (1935) stated that in 22 of the 27 analyzed examples of Lutembacher's syndrome the patient had been female. The striking predilection for the female sex in this complex far exceeds the 2:1 ratio of females to males in uncomplicated atrial septal defect Very likely the tendency for mitral stenosis of rheumatic origin to be more common in women is an important factor in determining the relatively greater frequency of Lutembacher's syndrome among female patients.

In the 24 cases of Lutembacher's syndrome reviewed by McGinn and White, one patient lived to the age of 74 years but 11 died before the age of 30 The average age

at death was 35 years, which these authors state is somewhat less than the average age at death for patients with mitral stenosis alone. Moreover, 35 years of age is less than the average age at death in cases of uncomplicated atrial septal defect. Therefore, one may conclude that in general it is advantageous for the patient with mitral stenosis not to have an associated atrial septal defect and likewise that it is better for the patient with atrial septal defect not to have an associated mitral stenosis.

Gibson and Roos stated that they believed that their patient with Lutembacher's syndrome, a boy aged 10 years, was the youngest reported to have died with this condition. The patient of Donnally died at the age of 2½ days but Gibson and Roos expressed the opinion that Donnally's case should not be classified as an example of Lutembacher's syndrome, since the patency of the foramen ovale was of incidental nature. In that case (see Congenital Mitral Stenosis, page 389) the mitral stenosis was considered to have been of congenital origin, an interpretation which seems valid because of the extreme youth of the patient.

In the typical case of Lutembacher's syndrome the mitral stenosis is usually, if not always, on a rheumatic basis. Though Lutembacher believed that the mitral stenosis in his patient, a woman aged 61 years, was congenital, present-day usage of the term does not require that the valvular disease be congenital. Indeed it is possible that in Lutembacher's patient the stenosis might have been on a rheumatic basis.

The atrial septal defect usually takes the form of a patent foramen ovale. Among 24 cases reviewed by McGinn and White the atrial septal defect was in the form of a patent foramen ovale in 18 of the cases. In four of the cases the defect was in the inferior part of the atrial septum and in one of the remaining two cases the foramen ovale was closed and the defect lay inferior to the entrance of the superior vena cava. The last case showed a patent foramen ovale and, in addition, a smaller defect ventral to the foramen ovale.

It appears that during the past decade the term "Lutembacher's syndrome" has fired the imagination of workers, with the result that more cases of this condition have been reported than probably exist. If the condition is to retain a specific connotation, caution must be exercised in evaluating a given case before making the diagnosis of Lutembacher's syndrome. Thus it must be established that an atrial septal defect exists of sufficient size to be significant, and there must be incontrovertible evidence of stenosis of the mitral orifice There has been an unjustified tendency to call any change in the mitral valve, when associated with atrial septal defect, mitral stenosis. It must be realized that many of the specimens of hearts with atrial septal defects are obtained from patients who have reached or passed middle life, and that thickening of the leaflets of the mitral valve is common at these age periods. Moreover in atrial septal defect *it is possible that the dilated left atrium* can cause stretching of the mitral valve ring and leaflets. A reaction to this mechanical stress may in itself result in some valvular thickening. Unless the mitral valve shows fusion of the leaflets at the commissures, it is to be seriously questioned that the mitral orifice is stenotic. It is obvious from the foregoing that the diagnosis of Lutembacher's syndrome requires not only accurate pathologic observation but also restraint. Certainly the clinical diagnosis of this condition must be made only after there are definite signs of mitral stenosis, in addition to evidence of atrial septal defect.

Among patients with atrial septal defect the difference between those with associ-

ated mitral stenosis, on one hand, and those without mitral stenosis, on the other, is only one of degree. Since an effect of the mitral stenosis is elevation of the left atrial pressure, the valvular disease, if present, would be responsible for a greater *difference in pressure between the two atria* than occurs without mitral stenosis The presence of mitral stenosis would then tend to cause a greater degree of shunt through the atrial septal defect than would exist in the absence of mitral stenosis The larger the shunt, the greater should be the degree of the secondary changes of atrial septal defect; namely, dilatation and hypertrophy of the right cardiac chambers and dilatation of the pulmonary vascular system Abbott (1915) published data on comparable cases showing that, in the case with mitral stenosis and atrial septal defect, *cardiac enlargement and pulmonary* arterial dilatation were of greater degree than in the case of atrial septal defect without mitral stenosis On the other hand Gibson and Roos (1935) reported two cases of atrial septal defect, one with mitral stenosis and one without They emphasized that the two hearts showed essentially the same degree of secondary effects. Whatever the cause of great cardiac enlargement in Lutembacher's syndrome, as compared to that in uncomplicated septal defect, there are cases of atrial septal defect without associated mitral stenosis which show as much enlargement of the right side of the heart and of the pulmonary trunk as is found in cases of Lutembacher's syndrome.

I have seen an instance of uncomplicated atrial septal defect in which the right-sided enlargement was of such magnitude as to allow an entire normal heart to be placed within the right atrium of the specimen. This case was reported by Erickson and Willius (1936); the patient was a man of 68.

In some reviews it is claimed that Lutembacher's syndrome complicates about 40 per cent of the cases of atrial septal defect The high figure may be explained by the tendency of some reviewers to categorize a case of atrial septal defect as having associated mitral stenosis if the original *article merely mentions* some thickening of the mitral leaflets My own opinion of the relative infrequency of Lutembacher's syndrome is supported by the fact that among the 27 cases of atrial septal defect in the pathologic collection of the Mayo Clinic there is only one case with mitral stenosis. Specimens of other cases show varying degrees of fibrous thickening of the mitral valve but no other features which would support a pathologic diagnosis of stenosis of the mitral orifice. Cosby and Griffith (1949) found no examples of the syndrome among 19 cases of atrial septal defect studied at necropsy Among the 45 hearts with atrial septal defect obtained from four Boston hospitals, Gelfman and Levine (1942) found five with coexisting rheumatic disease The authors considered *only two of these as examples of a true* Lutembacher syndrome These findings are of considerable importance in supporting the concept that Lutembacher's syndrome is infrequent, since the material on which Gelfman and Levine reported covered periods which aggregated 144 hospital years.

The case of Kurz and Fischer (1949) deserves some mention Their patient was a man, aged 47 years, with an atrial septal defect and bacterial endocarditis of the mitral valve. Though Kurz and Fischer claimed that their case was also one of Lutembacher's syndrome, the published photograph of the mitral valve fails to reveal any of the chordal and valvular adhesions characteristic of mitral stenosis.

Mention has already been made of the case of Tinney and Barnes (1942), which is quoted as an example of Lutembache' syndrome complicated by bacterial e carditis. As pointed out, restudy o

heart indicates that the deformity of the mitral valve is congenital and stenosis does not seem to be a feature of the deformity.

Paradoxic Embolism. Paradoxic or crossed embolism is a phenomenon of embolism occurring in the systemic arterial circulation secondary to an embolic source in the right side of the heart or in one of its tributary veins This occurrence depends on the existence of some communication between the two sides of the heart Though patent ductus arteriosus and ventricular septal defect may constitute such communications, the chief route for crossed emboli is through an opening in the atrial septum Young and associates in 1948 made a review of the literature on paradoxic embolism They stated that among 40 cases of this condition which they reviewed, 33 were associated with patent foramen ovale, the remaining seven with ventricular septal defect The historical features of this phenomenon have been reviewed by several authors (Abbott, Lewis and Beattie, 1923, Thompson and Evans, 1930, Hirschboeck, 1935, Ingham, 1938).



Figure V-8A Paradoxic embolism The posterior walls of the atria have been cut away In the right atrium there is a long embolus, the forward portion of which extends through a probe-patent foramen ovale into the left atrium From a woman 48 years of age

The type of defect in the atrial septum may be either a probe-patency or a true patency (Beattie, 1925) In the section on probe-patency it has been stated that during conditions of normal cardiovascular function there is little if any passage of blood between the atria, and any passage that occurs is limited to flow from right to left. This is so because normally the pressure in the left atrium exceeds that in the right atrium and thus the valve of the foramen ovale is held against the rest of the atrial septum, preventing escape of the left atrial blood into the right atrium. When, for any reason, there is elevation of the right atrial pressure to a level exceeding that in the left atrium, blood will flow across the septum from the right atrium into the left atrium (Gross, 1934). Pulmonary embolism is the basic cause for elevated right atrial pressure in about half of the cases of paradoxic embolism (Thompson and Evans). If after the right atrial pressure becomes elevated there are embolic particles in the right atrial chamber, crossing of emboli into the left side of the heart may occur (Figures V-8A and B).

In a given individual, when true functional patency of the atrial septum is present, paradoxic embolism is more likely to occur than when mere probe-patency is present. Yet in the over-all picture of paradoxic embolism, probe-patency is the more common basis for interatrial flow than is true patency. This seems to be explained by the much greater incidence of probe-patency than of true atrial septal defect

Another point of interest is that, compared to the frequent occurrence of probe-patency and of emboli in the right atrium, the incidence of paradoxic embolism is extremely low. The reasons for this were explained by Thompson and Evans. In the first place, the initial occurrence of pulmonary embolism may be rapidly fatal, death occurring before other emboli enter



Figure V-8B Paradoxic embolism Folded thrombus caught in foramen ovale Seen from left atrial aspect Patient was a 52-year-old man with periprostatic venous thrombosis, embolism to lungs and paradoxic embolism to kidneys (WCGH, 45 A 386)

the right atrium If the patient survives the first attack of pulmonary embolism during which more than one-third of the pulmonary circulation had become occluded to effect an elevation in right atrial pressure, he must have a second attack to suffer from paradoxic embolism. If he does have a second attack, the embolus must be small enough to be received by the channel through the atrial septal complex. It is to be emphasized that whereas in about 20 to 25 per cent of adults there is a retention of the fetal interatrial channel in the form of probe-patency, there has usually been some closing of the tract so that it is considerably narrower than it would be were there no closure. All of these facts explain the relative rarity of paradoxic embolism

In the majority of cases of paradoxic embolism the embolus is composed of bland thrombotic material but embolization of tumor and of infected material is also possible Thompson and Evans emphasized justifiably that when paradoxic embolism of either tumor or bacteria is suspected, much consideration must be given to the possibility that there had been embolism to the lungs and that the tumor or infectious process had spread from the lungs by way of the pulmonary veins to the left side of the heart It is pertinent to add that thrombotic material also might pass to the left side of the heart after having been formed in pulmonary veins. This suggests the desirability of routine careful examination of the pulmonary veins during every necropsy, and emphasizes the necessity of such scrutiny when arterial emboli are present

The most common site of arterial occlusion secondary to paradoxic embolism is one of the cerebral arteries, usually one of the middle cerebral arteries or a branch of these Usually, several arteries are involved, the renal, splenic and coronary arteries sharing in the process Occasionally the arteries of the neck or of either the upper or lower extremities are also involved

In the discussion of bacterial endocarditis complicating atrial septal defect, reference was made to the case of Geiger and Anderson (1947) in which it is conceivable that emboli originating on the mitral valve crossed from the left atrium into the right atrium. If the case is interpreted correctly, it is quite unusual in that paradoxic embolism was in a left-to-right direction, the reverse direction from that of the usual case of crossed embolism.

Premature Closure of Foramen Ovale

Early workers, basing their conclusions largely on the structure of the fetal heart, concluded that practically the entire stream of inferior caval blood passed through the foramen ovale to the left

atrium. More recent studies (Barcroft, Barclay, Barron and associates, 1935-1947) indicate that although a substantial proportion of the inferior caval current follows this route some of it enters the right atrium, there to mingle with the blood entering from the superior vena cava. Leaving aside the still controversial matter of what proportion of the inferior caval current passes directly to the left atrium, it is clear that the left side of the fetal heart must receive a considerable proportion of its intake by way of the valvular mechanism at the foramen ovale. This shunt is obviously a necessary phenomenon for maintenance of right-left balance in the prenatal development of the heart and for its normal postnatal functioning. These statements are borne out by the rare cases in which the foramen ovale fails to remain open throughout intra-uterine life.

The appearance of the atrial septum may vary among cases classified as *premature closure of the foramen ovale*. The septum may show a properly formed foramen ovale but the opening may be closed by a membrane. This condition may be interpreted as a fusion of the valve of the foramen ovale with the interatrial septum secundum. The other appearance is characterized by absence of the foramen ovale; that is, the septum secundum appears to have grown beyond its normal bounds and no opening (foramen ovale) is left. The associated changes reflect the absence of normal filling of the left side of the heart during fetal life and the concomitant overburdening of the right side of the heart. Thus, the chambers of the left atrium and ventricle are noticeably smaller than normal and the right-sided cardiac chambers are larger than normal. The right ventricular wall is hypertrophied and the ductus arteriosus is unusually wide.

Normally in the fetus the left atrium receives blood from two sources: (1) from the lungs by way of the pulmonary veins; and (2) from the right atrium through

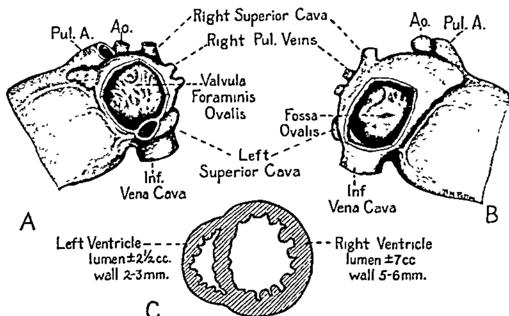


Figure V-9 Premature closure of the foramen ovale in an infant. (From Patten, 1938, by permission of the author and *American Journal of Pathology*.)
A. The valve of the foramen ovale is adherent to the septum.
B. The fossa ovalis is represented as a small slit.
C. The large right ventricle and the small left ventricle are the consequence of lack of transatrial flow in the fetus.

the foramen ovale. The development to normal size of the left cardiac chambers seems dependent upon blood entering the left atrium from both these routes. When the foramen ovale closes during fetal life the left atrium receives blood only from the pulmonary veins. This volume is evidently insufficient to cause the left-sided cardiac chambers to develop to their normal capacities. As will be explained later, this underdevelopment is probably the basis for some of the postnatal functional disturbances resulting from premature closure of the foramen ovale.

More directly related to fetal well-being is the effect upon the right side of the heart. This accommodates to the greater volume of blood that it must carry, but embarrassment of the right ventricle is a potential danger. Right-sided cardiac failure may develop during fetal life When this happens, the fetus shows the same signs of chronic cardiac failure as are seen in congestive failure during postnatal life. There are marked edema of the skin and subcutaneous tissues, collections of fluid in the serous cavities and chronic passive congestion of the liver and spleen. Hydramnion may also be associated.

When cardiac failure develops during fetal life, stillbirth may result or the infant born alive may be markedly edematous. This was one of the features of the case of premature closure of the foramen ovale which Benner (1939) mentioned in his review. A second clinical manifestation of the condition may be that the infant appears normal at birth but cyanosis develops in the neonatal period. This clinical manifestation may be the result of the underdevelopment of the left atrium and ventricle. It may be explained as follows: When the left side of the heart is smaller than normal it may not be able to receive a normal amount of blood. This would raise the pressure within the pulmonary vessels If this exceeds the pressure within the aorta and if the ductus arteriosus remains open, there will be a shunt of venous blood into the aorta. If on the other hand the ductus closes, difficulty may be caused by pulmonary vascular stasis resulting from inability of the pulmonary veins to empty properly, coupled with the constant forcing by the right ventricle of more blood into the lungs Under such conditions life soon fails.

The developmental basis for premature closure of the foramen ovale has already been suggested. Theoretically it may arise in two different ways

1 Septum secundum may overgrow to such an extent that no foramen ovale is left The cases of Lehman (1927) and of Patten (1938) are characteristic examples of this form of premature closure (Figure V-9). It seems worth reemphasizing the importance attached by Patten to the fact that this malformation is a result of local overgrowth, rather than explaining it on an alleged basis of a "developmental arrest"

2 The premature closure might result if, after normal formation of the atrial septal complex, the valve of the foramen ovale became fused to septum secundum, as it does in the majority of persons some time after birth. The hearts of those newborn infants in which the tract from the foramen ovale into the left atrium is present but is narrower than normal could be said to represent such a phenomenon

The second case of Benner, and that of Read and Krumbhaar (1932), could be considered examples of this type of premature closure The case of Ludwig (1912) deserves special mention. His patient was a newborn female with marked edema of the tissues at birth. In addition to closure of the foramen ovale there was mitral stenosis

Whatever the cause of the valvular deformity, whether developmental or inflam

matory, its presence in the neonatal period must be accepted as evidence of having developed during fetal life. With valvular stenosis present it is conceivable that the left atrial pressure during fetal life might have been greater than normal and possibly greater than the right atrial pressure. Such a condition would be similar to postnatal atrial pressure relationships, for in fetal life, as after birth, there would be a tendency for the valve of the foramen ovale to be pressed against the interatrial septum secundum and to fuse with this component of the atrial septal complex Similar explanations are applicable to the cases of McIntosh and of Edwards and DuShane (1950). In these there was congenital mitral atresia associated with premature closure of the foramen ovale (see Congenital Mitral Atresia, page 386).

Remnants of the Valves of the Sinus Venosus. Chiari's Network

In the right atrium of many normal hearts there are remnants of the valves of the sinus venosus. It is recalled that, as the developing sinus venosus is incorporated into the wall of the right atrium, the valve leaflets of the sinus venosus (the valvulae venosae) project into the right atrial chamber. The right valve normally becomes developed into the valve of the inferior vena cava (the eustachian valve) and the valve of the coronary sinus (the thebesian valve). This evolution of two valves from one involves a considerable reduction in relative extent, and a division into the two components of what remains of the right venous valve. Normally the left valve suffers even greater reduction and its remains blend with the septum secundum of the interatrial septal complex. Yater (1929) has reviewed the literature on the fate of the valvulae venosae and reported on a study of a large number of hearts of adults from the point of view of identifying structures related to these valves. Most of the comments that follow are taken from his comprehensive and excellent review. In a study of a series of hearts he was able to find a variety of changes illustrating gradual progression from unusually large but structurally normal thebesian and eustachian valves to those which showed features due to embryologic deviation. In a series of 120 hearts Yater found 17 cases in which a ridge was all that denoted the previous existence of the right venous valve except for the thebesian valve. In this group of 17 hearts there were 16 which showed the thebesian valve and one that did not.

The most common condition of the eustachian valve occurred in 69 of Yater's cases. This showed a crescentic valve which in some cases was thin and transparent and distinct from the margin of the inferior vena cava. In other cases it was firm and merged with the rim of the inferior vena cava and the wall of the atrium. In 22 cases there was a fenestrated semilunar membrane containing one or several small openings. In most of these cases the valve was thin. In seven cases the valve of the inferior vena cava was formed in part or entirely by a network of fibers resembling a cobweb. In all the foregoing cases the eustachian and thebesian valves were distinct from each other. In two of the cases in Yater's 120, the eustachian and thebesian valves formed one membrane. In three cases, instead of thebesian and eustachian valves, there was a Chiari network. The details of this network will be described subsequently.

It is evident that the formation of the thebesian and eustachian valves always entails a considerable reduction in the primitive right venous valve from which they are molded. In many instances this reduction progresses so far that the thebesian and the eustachian valves are scarcely more than vestigial folds. Not infrequently the resorptive process by which they are

shaped results in the destruction of small areas of the part that persists, thus leaving fenestration in these valves. In some instances the fenestrations may be so extensive as to leave the valvular tissue represented only by delicate threadlike strands. According to Yater, in keeping with Chiari's original description, the mere presence of fenestrated thebesian or eustachian valves should not be considered as representing Chiari's network. In all of Chiari's cases some of the fibers of the network had some attachment either to the atrial wall near the upper portion of the crista terminalis or to the atrial septum. Therefore, the term "Chiari's network" should probably be applied only to reticular formations that possess threads with such widespread attachments. Thus, Chiari's network may be defined as a network of fine or coarse fibers in the right atrium, its attachments extending from the region of the crista terminalis above, to the thebesian and the eustachian valves, or even to the floor of the right atrium in the region of the orifice of the coronary s[illegible] below (Figures V-10A and B).



Figure V-10A Right atrium Chiari's network One band of the network (right upper part of figure) is attached to the crista terminalis near the mouth of the superior vena cava From a woman 74 years of age.



Figure V-10B Chiari's network From a man 69 years of age (Drawing by Louise Horne, Wayne County General Hospital, WCGH, 45 A 354.)

In examining a large series of hearts in the anatomic dissecting room, Wright and his associates (1948) made observations similar to those of Yater. In nine specimens among 512 hearts studied, Wright and associates found fibrous cords attached to the free edge of the eustachian valve. In eight of these the opposite extremities of the cords were attached to the atrial wall but not to the crista terminalis. In the ninth case the cords were attached to the crista terminalis. In keeping with the tenets of Yater, Wright and his associates expressed the opinion that in only the last case cited was there a Chiari network.

The functional significance of Chiari's network is probably of no importance in the usual case. Several reported cases mentioned in Yater's review were instances in which there was pulmonary embolism and in which thrombotic material was attached to the network. In most of these cases it was found that thrombi were also present in the veins of the inferior ex



Figure V-10C Remnants of left valve of sinus venosus attached to septum secundum and the posterior portion of the fossa ovalis From a man 38 years of age

tremities. The interpretation that the foreign material in the valve membrane was an embolus caught in the network rather than a thrombus starting at this point seems to be plausible. In one of his cases Chiari (1897) thought that pulmonary embolism had resulted from thrombi originating in the network.

Remnants of the left valvula venosa are frequently present in normal hearts. These are represented by a reticulum of fibers, at times resembling chordae tendineae, attached to the right side of the atrial septum in the region of the posterior half of the fossa ovalis. As a rule these flattened cords or bands do not lie free but are intimately attached to the atrial septum (Figure V-10C). In rare cases portions of the filaments may extend freely into the right atrial chamber and in a very rare case, such as that of J. M. Swan (1898), there may be a membrane that is attached to the posterior portion of the fossa ovalis and extends as a valve flap into the right atrial chamber. Although Swan interpreted his case as representing a Chiari network, Yater's interpretation that it represents remnants of the left valve of the sinus venosus seems to be the correct one. Remnants of the left valve of the sinus venosus are usually of no functional consequence.

It is of passing historical interest that, according to Yater, Przewoski in 1896 had described networks of fibers in the right atrium near the mouths of the great veins and along the limbus of the fossa ovalis. He expressed the belief that the networks represented remnants of the venous valves of the embryo. This interpretation antedated by a year Chiari's more exact descriptions and interpretations.

Aneurysm at Fossa Ovalis

Occasionally the floor of the fossa ovalis (septum primum) bulges into either the right or the left atrial chamber (Lang and Posselt, 1934). When this happens, the foramen ovale is usually closed and the bulge of the floor of the fossa results because the floor is redundant and the pressure in one atrium is greater than in the other. Under ordinary circumstances it would be expected that the bulge would be toward the right, since normally the left atrial pressure exceeds the right atrial pressure. Cases such as Canavan's (1940), in which the aneurysm bulged into the left atrium, have been explained on the basis of cardiac failure, which in turn resulted in elevation of right atrial pressure.

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Congenital Malformations

B. Malformations of the Ventricular Septal Complex

DEFECTS OF THE VENTRICULAR SEPTUM

Defects of the Muscular Portion

Defects of the ventricular septum may involve either the muscular or the membraneous portion Defects of the muscular septum are usually single but may be multiple They are far less common than those of the pars membranacea. The defects may occur in any area of the muscular septum but usually lie about midway between its basal portion and the apex. I have personally observed six examples of this malformation. In one case the openings in the ventricular septum were multiple and the defect was associated with atresia of the mitral orifice, premature closure of the foramen ovale and an anomalous communication between the left atrium and the left innominate vein (Figure V-11, see Mitral Atresia, page 386, for discussion of this case). In the remaining five cases (three of the patients were infants and two were adults) there were no associated cardiovascular malformations and the defect in each instance was single. The defects in the infants were ovoid in shape while those in the adults were small and linear, their upper and lower margins being almost in apposition (Figure V-12*a* and *b*) This meager evidence suggests that defects of the muscular portion of the ventricular septum may become smaller, if indeed they do not become closed, as the ventricular septum grows. Functionally defects of the muscular and of the membranous portions are essentially alike, though it is possible that a defect of the muscular part may become reduced in size during ventricular systole. If that is so, a defect of the muscular part which has the same size as a membranous defect in the postmortem specimen might not have allowed as large a shunt during life.

Mason and Hunter (1937) reported three cases with defects of the muscular part of the ventricular septum In two of the cases the defects were the sole malformations of the ventricular septum and in the third case the defects involved both the muscular and the membranous portions. Hemsath and associates (1936) reported a similar case in a girl aged three months, the membranous defect was associated with a deformed septal leaflet of



Figure V-11 Multiple defects of the muscular part of the ventricular septum viewed from the left ventricle The membranous septum is intact From a female infant aged 27 days with mitral atresia and a levoatriocardinal vein (From Edwards, J E, and DuShane, J W *Arch Path*, 49 517-537, 1950)

the tricuspid valve. The patient of Weiss (1927) was a man aged 79 years with a defect of the muscular part of the ventricular septum measuring 2 0 cm. Though in this last case the evidence is in favor of a *congenital origin, one must be cautious in* determining the basis for defects of the muscular portions of the ventricular septum. Determination that a given defect is of congenital origin rests primarily on demonstration that there is no associated disease of the myocardium which could cause the communication. The most common cause of acquired communications between the ventricles is perforation following myocardial infarction Less common causes are myocardial abscess and traumatic disease. Usually the underlying disease which causes the acquired interventricular communication is of such serious proportions that the patient dies at a time when the edges of the defect are still raw.

The developmental basis for defects of the muscular portion of the ventricular septum has been discussed by Wimsatt and Lewis (1948) whose paper also contains a bibliography on this subject. Defects of the muscular portion of the ventricular septum are probably related to the normal *embryonic condition in which there is ex*tensive trabeculation of the ventricular septum as well as of the ventricular walls. In young embryos some of the intertrabecular spaces represent open, though tortuous, communications between the two ventricles (see Chapter II). Should any of these fail to close, defects of the muscular part of the ventricular septum would result. Beyond this basic developmental influence, Wimsatt and Lewis have ex*pressed the opinion that mechanical fac*tors may lead to retention of communications between the two ventricles at the level of the muscular septum. In a heart that I have seen with multiple openings in the muscular septum, mitral atresia was present, all of the incoming blood had collected in the right atrium and then flowed through the tricuspid valve into the right ventricle, and the membranous portion of the ventricular septum was closed This *resulted in unusual force being exerted* against the ventricular septum by blood within the right ventricle (Figure V-52*b*) It is possible that this force caused the interventricular openings of the embryo to persist. Indeed, this was the only route by which the left ventricle could receive blood.

Defects of the Membranous Portion (Pars Membranacea)

In Chapter II on Development of the Heart it was related that the membranous portion of the ventricular septum has a complicated origin involving contributions from three sources: (1) a downgrowth of the ridges which partition the conus region of the ventricles; (2) an ingrowth of tissue from the right tubercles of the endocar-



Figure V-12. *a* Left ventricular aspect of a single muscular ventricular septal defect in a male infant five and one-half months old The defect is ovoid (From Dry, T J, Edwards, J. E, Parker, R L, Burchell, H B, Rogers, H. M, and Bulbulian, A H. *Postgrad. Med*, 4: 231-264, 1948. Reproduced by permission of *Postgraduate Medicine.*)

b Left ventricular aspect of a single muscular ventricular septal defect in a man aged 65 years The margins of the defect, seen in the central portion of the figure, are in apposition, suggesting that the size of the defect is less than at an earlier stage in the patient's life

dial cushions of the atrioventricular canal, and (3) endocardial cushion tissue at the crest of the muscular part of the ventricular septum It is evident from this composite origin that, on one hand, defects of the membranous portion of the ventricular septum may be the sole defect in a given heart or that, on the other hand, the defect may be part of a more complicated congenital malformation. In this section we are concerned with those cases in which a defect of the membranous part of the ventricular septum is the sole malformation. Such a defect is often called an uncomplicated ventricular septal defect.

As previously stated, defects of the membranous portion of the ventricular septum are far more common than defects of the muscular portion. In the usual case of ventricular septal defect, the interventricular communication is at the level of the membranous portion.

In contrast to defects in the muscular part of the ventricular septum, which may be multiple, defects of the membranous part are almost invariably single. From the left side the defect is seen to occupy the superior portion of the ventricular septum, lying immediately inferior to the aortic valve (Figure V-13*a* and *c*). On the right side the defect opens into the right ventricle in the vicinity of the septal leaflet of the tricuspid valve (Figure V-13*b* and *d*). Frequently the septal leaflet and chordae of the tricuspid valve are clearly visible through the defect from the left ventricular side (Figure V-13*a*). At times tricuspid chordae tendineae may be inserted into the margin of the defect. This is not surprising, since the same tissue which contributes to the membranous portion of the ventricular septum also contributes to the tricuspid valve. The septal leaflet of the tricuspid valve may be de-



Figure V-13 Defect of the membranous portion of the ventricular septum in a female infant 11 days old

a From the left ventricular aspect the defect is seen just below the aortic valve Chordae tendineae and part of the septal leaflet of the tricuspid valve are visible through the defect Several of the chordae tendineae are attached to the margins of the defect (From Edwards, J E, *Postgrad Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

b From the right ventricular aspect the defect is seen in close relationship with the septal leaflet of the tricuspid valve From this view the defect is partly hidden by the valve Incidental telangiectases are present in the tricuspid valve leaflets

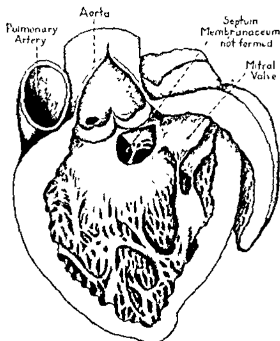


Figure V-13*c* Ventricular septal defect viewed from the left, showing tricuspid valvular tissue through the defect

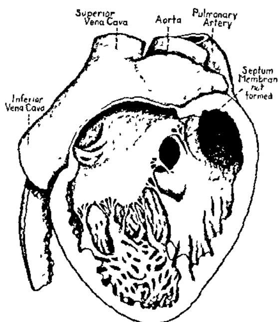


Figure V-13d Ventricular septal defect, viewed from the right ventricle. The defect is partly overhung by the septal leaflet of the tricuspid valve. (*c* and *d*, from drawings prepared by Dr B M. Patten)

formed (Weinstein, 1926; Mason and Hunter, 1937).

The endocardium of the left ventricle immediately inferior to the ventricular septal defect frequently shows a localized fibrous thickening. The thickening appears as a sheet of firm gray tissue which rises above the general endocardial surface. This elevation is particularly noticeable at the lower margin of the fibrous lesion, giving the appearance of an endocardial pocket. The localized endocardial thickening, which has been called a systolic pocket, is probably related to the impact of blood flowing from the left ventricle. Evidently there is a peculiar directional nature to this stream which traumatizes the endocardium. In addition to the endocardial thickening in the left ventricle there may be fibrous thickening of the margins of the defect. This too seems to be a reaction to trauma caused by blood forcibly ejected from the left ventricle through the defect. It will be recalled that the bundle of His lies in the crest of the muscular portion of the ventricular septum. Stated in another way, the bundle of His lies immediately inferior to defects of the membranous portion of the ventricular septum. Therefore, fibrous tissue developing in the lining of a defect of the pars membranacea may extend to involve the underlying conduction bundle. Since this change is one that occurs over a period of time, an infant with a defect in the membranous portion of the ventricular septum may be born with normal cardiac conduction, only to develop at a considerable time after birth atrioventricular conduction defects and even complete heart block (Burchell, 1949).

Some patients with ventricular septal defect may be born with complete heart block (Ash and associates, 1939). In the case of Massey (1948) it was noted during intra-uterine life of the infant that the fetal cardiac rate was slow. A subsequent electrocardiogram of the infant revealed complete heart block.

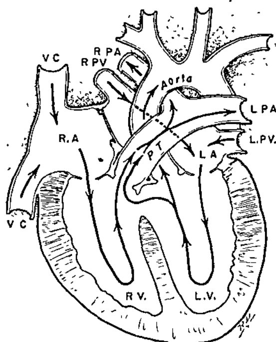


Figure V-14 The intracardiac circulation in ventricular septal defect *L A*, left atrium, *L P A*, left pulmonary artery, *L P V*, left pulmonary vein, *L.V*, left ventricle, *P T*, pulmonary trunk, *R A* right atrium, *R P A*, right pulmonary artery, *R P.V*, right pulmonary vein, *R V.*, right ventricle, *V.C*, vena cava

Tucker and Kinney (1945) reported the unusual association of a membranous ventricular septal defect in a mother and her offspring.

Functional Disturbances and Complications of Ventricular Septal Defects. In spite of the presence of an interventricular opening, a differential pressure between the left ventricle and the right ventricle is maintained. Consequently, during ventricular systole there is ejection of some of the left ventricular blood into the right ventricle (Figure V-14). Studies by means of cardiac catheterization on patients with uncomplicated ventricular septal defects reveal that about half of the left ventricular output flows through the septal defect into the right ventricle (Baldwin *et al.*, 1946; Dexter *et al.*, 1947; Handelsman *et al.*, 1948; Burchell *et al.*, 1948; Cournand *et al.*,

1949). As a rule there is no associated significant elevation of pulmonary blood pressure. The case of Burchell and associates is an exception in that pulmonary hypertension existed in a boy aged 12 years with evidence of a ventricular septal defect on cardiac catheterization.

Pulmonary hypertension in a case of ventricular septal defect may mean one of two things. In the first instance the patient may have an ordinary ventricular septal defect which after birth has become complicated by occlusive vascular changes in the lungs. Such a complication is uncommon. The other explanation is that the patient does not have the ordinary ventricular septal defect but presents the Eisenmenger complex. The latter condition will be discussed at greater length in another section. Briefly, however, this complex involves a membranous septal defect and origin of the aorta partly, or in rare instances completely, from the right ventricle; there is no concomitant pulmonary stenosis, pulmonary hypertension is characteristic and is probably present to some degree from the time of birth; and venous blood is delivered to the aorta Delivery of venous blood to the aorta may not be of sufficiently great proportion, particularly in younger patients, to cause visible cyanosis, but there is always some degree of desaturation of the arterial blood.

This brings up the pathologic distinction between ventricular septal defect (maladie de Roger) and the Eisenmenger complex. Between the extremes of characteristic examples of each of these two conditions there are certain cases that are difficult to evaluate on examination of the specimen. In most instances of membranous ventricular septal defect one can pass a probe from the right ventricle through the septal defect into the aorta. This in itself should not be considered to constitute dextroposition of the aorta. For the latter diagnosis, there should be definite origin of at least part of the aorta from the right ventricular wall. In cases with minor degrees of aortic dextroposition there are certain individuals who clinically have failed to show pulmonary hypertension and desaturation of the systemic arterial blood This apparent discrepancy between the clinical features and the pathologic findings probably depends on variations in the way the blood streams from the two ventricles impinge upon each other at the arterial outlets For example, the stream from the left ventricle may emerge through the septal defect in such a manner that it deflects the right ventricular blood away from the aortic orifice. If this occurred there would be a minimal amount of venous blood entering the systemic circuit. Such cases usually fail to show right ventricular hypertrophy A case of ventricular septal defect with minor degrees of dextroposition of the aorta but without significant right ventricular hypertrophy and without the usual clinical manifestations of the Eisenmenger complex should in all probability be classified as an unusual form of ventricular septal defect rather than as an example of the Eisenmenger complex

It will be recalled that the septal leaflet of the tricuspid valve overhangs the right aspect of the ventricular septal defect (Figure V-13*b*). Consequently, this leaflet may be traumatized by the jet of blood which emerges through the ventricular septal defect. As the septal leaflet of the tricuspid valve is thrown cephalically during systole, it moves away from the ventricular septal defect and the jet of blood then tends to strike the ventral wall of the right ventricle. These two points of trauma by the blood forced through the ventricular septal defect are of consequence in that they may act as foci for the origin of bacterial endocarditis. This will be considered subsequently.

The blood which enters the right ven-

tricle from the left ventricle is mixed with venous blood in the right ventricle (Figure V-14). The mixture is then pumped into the pulmonary trunk to pass through the lungs and return to the left side of the heart Some of the arterialized blood again passes through the ventricular septal defect, the right ventricle and the pulmonary vascular system. This functional disturbance places a burden on both ventricles There is a tendency for each ventricle to become somewhat hypertrophied. As a rule it appears that each ventricle hypertrophies in proportion to its usual ultimate postnatal size. This probably accounts for the fact that although there may be right or left axis deviation in the electrocardiogram in ventricular septal defect, usually the electrocardiogram shows no predominance of either ventricle Reference has also been made to the association of conduction disturbances with this malformation Patients with ventricular septal defect may bear the effects of the shunt well, and some live to adult life.

In the Mayo Clinic collection of 212 specimens with major cardiovascular malformations there are 26 specimens classified as ventricular septal defect. Five of the defects were in the muscular portion of the septum An additional case with multiple defects in the muscular portion of the septum is classified primarily as an example of congenital mitral atresia. In the oldest four of the 21 cases with defects involving the membranous portion of the septum the patients were aged 12, 13, 21 and 55 years, respectively, at the time of death. Bacterial endocarditis complicated two of the cases, in one the patient was a girl aged five years and in the other, the patient was a man aged 21 years (Figure V-15*a* and *b*). In each the septal defect involved the membranous portion. The defect in the girl aged five years was unusual in that its right side communicated with the right atrium rather than with the right ventricle (see Left Ventricular-Right Atrial Communications, page 302).



Figure V-15 Subacute bacterial endocarditis complicating ventricular septal defect in a man 21 years old

a In the left ventricle the vegetations are near the defect and on the aortic valve. (From Edwards, J E. *Postgrad. Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

b In the right ventricle the vegetations involve the margins of the defect and the neighboring part of the ventricular wall

Abbott in 1936 reported that the average age at death was 14.5 years. Cardiac failure is one of the major causes of death. Another important factor is bacterial endocarditis which is particularly frequent in membranous septal defects. The bacterial endocarditis tends to develop along points of trauma (Furlong, 1944). The in-

flammation may start on the margins of the septal defect, on the septal leaflet of the tricuspid valve or on the ventral wall of the right ventricle. From these sites the infection may extend to other points Thus, from the left ventricular side it may extend to the aortic valve. The importance of bacterial endocarditis as a complication of ventricular septal defect is stressed by Abbott (1925) and by Gelfman and Levine (1942). Of 555 cases of congenital cardiac disease of clinical significance which Abbott analyzed, there were 40 examples of ventricular septal defect of which 16 (40 per cent) were complicated by bacterial endocarditis.

Gelfman and Levine studied 453 cases of congenital cardiac disease of which 35 were complicated by bacterial endocarditis. There were 164 patients of all ages with ventricular septal defect which in 17 instances or approximately 10 per cent were complicated by bacterial endocarditis. In 181 of the total number of cases, the patients were two years of age or older at the time of death; 31 of these 181 had a ventricular septal defect and in 13 of the 31 cases (42 per cent) the defect was complicated by bacterial endocarditis This incidence of bacterial endocarditis complicating ventricular septal defect corresponds to that reported by Abbott In only five of the cases of Gelfman and Levine in which the patients were two years of age or older did the bacterial infection involve the margins of the defect.

The higher incidence of bacterial endocarditis complicating ventricular septal defect in the older group bears out, in a broad way, the maxim that the longer the patient with congenital cardiac disease survives, the greater his chance of developing bacterial endocarditis. It probably means that certain types of cardiac disorders constitute fertile soil for the development of bacterial endocarditis. The longer such patients live, the more contact they have with bacteria and so their chances of acquiring a complicating infection are correspondingly increased

It is interesting to note the occurrence of 17 cases (10.4 per cent) of bacterial endocarditis in ventricular septal defect among patients of all ages as compared with 18 such infections (6.2 per cent) in all other types of congenital cardiac disease studied by Gelfman and Levine This supports the concept expressed by Furlong and others that those hearts in which the shunted blood has a traumatizing effect are more likely to develop a complicating infection than hearts in which there is no such traumatizing influence.

Some indication of the incidence among adults of bacterial endocarditis in ventricular septal defect as compared to the overall incidence of subacute bacterial endocarditis may be gained from a paper of Christian (1941) Among 150 adults with subacute bacterial endocarditis there were eight in whom the underlying basis for the infection was believed to be a congenital cardiac malformation In three cases confirmed by autopsy the endocarditis was secondary to malformations of the aortic cusps There were five cases which were not confirmed by necropsy but which clinically were believed to be examples either of ventricular septal defect or of patent ductus arteriosus.

Blumgart (1933) has emphasized that since the shunt in ventricular septal defect is from the left ventricle to the right ventricle, the embolic phenomena of bacterial endocarditis usually occur in the pulmonary circulation rather than in the systemic circulation He pointed out that in bacterial endocarditis of the right side of the heart peripheral emboli and positive blood cultures of the peripheral blood may be absent. There is a characteristic syndrome of bacterial endocarditis involving the right side of the heart which includes the following features. (1) presence of a car-

diac lesion in a right cardiac chamber; (2) evidence of generalized infection, (3) no evidence of peripheral emboli in the greater circulation, but instead symptoms and signs of protracted pulmonary infection caused by multiple septic pulmonary infarcts. Only in far-advanced stages of disease, when there is necrosis of the septic pulmonary infarcts, do organisms tend to reach the systemic circulation.

Blumgart thought that a left-to-right shunt had been present in his patient, a girl aged 13 years with ventricular septal defect and bacterial endocarditis, on the evidence of an endocarditis that involved the tricuspid valve and the right margins of the septal defect. The left side of the defect was uninvolved by the bacterial inflammation.

Among unusual complications of ventricular septal defect are paradoxic embolism (see page 278) and cerebral abscess developing in the absence of bacterial endocarditis.

Defects Involving the Entire Ventricular Septum

Cor Triloculare Biatriatum. If the entire ventricular septum is absent and the atrial septum is present, the heart is three-chambered and is called *cor triloculare biatriatum*. Not only should hearts with absence of the entire ventricular septum be thus classified but also those having a rudimentary ventricular septum and a communication between the two ventricles of such proportion as to produce a functional condition equivalent to absence of the ventricular septum (Favorite, 1934). Usually if there is no ventricular septum, both the tricuspid and mitral orifices communicate with the inflow portion of the common ventricle (Figure V-16*a*). At the outflow portion there is frequently a dividing muscular band (Taussig, 1939). This runs from the base of the dorsal wall to the ventral wall of the common ventricle. While at times considered to be a rudimentary ventricular septum or an aberrant crista supraventricularis, Patten (personal communication) thinks it more probable that it represents a partial persistence of the cono-ventricular flange of the young embryonic heart (Figure II-20). This muscular band divides the outflow tract of the common ventricle into two portions. The smaller is usually on the right and in a subaortic position, the larger is usually dorsal and subpulmonary. This division of the outflow tract has at times been interpreted as representing two ventricles. As indicated, this division is better interpreted as merely a partitioning of the outflow tract of a common ventricle. Occasionally the subaortic outlet may be so narrow as to constitute an important barrier to the flow of blood from the common ventricle into the aorta (Figure V-16*a*).

Transposition of the great vessels is usually associated with this defect. The aorta lies in front and parallel to the pulmonary trunk and, as a rule, on a plane somewhat to the right of that of the pulmonary trunk (Figure V-16*b*). Occasionally the aorta lies somewhat to the left of the pulmonary trunk (Kornblum, 1935; Glendy *et al.*, 1944). Cor triloculare biatriatum without transposition of the great vessels is exceedingly rare.

Drey, Strauss and Gray (1938) reported a case of cor triloculare biatriatum without transposition of the great vessels. They stated that only one other case similar to theirs, the Holmes (1824) heart, had ever been reported. In the Mayo Clinic collection of 212 specimens with major congenital cardiac malformations there is one example of a single ventricle without associated transposition of the great vessels (Figure V-17*a* and *b*). While cor triloculare biatriatum is uncommon, it is observed more frequently than cor biloculare.

In the Mayo Clinic collection there are nine examples of cor triloculare biatriatum.



Figure V-16 Cor triloculare biatriatum with transposition of the great vessels in a female infant five months old

a An incision from a right anterior position to a left posterior one divides the single ventricle and the great arteries The two halves have been swung open like a hinge In the photograph to the left are shown probes in the tricuspid and mitral orifices The aorta lies ventral to the pulmonary trunk and is narrower than the latter A muscular bundle, the crista supraventricularis, divides the outflow part of the single ventricle into a wide subpulmonary tract and a narrow subaortic tract

b The heart, lungs, and great vessels There is transposition of the great vessels, the relatively narrow ascending aorta lying to the right and in front of the wide pulmonary trunk Also, that part of the aortic arch between the origins of the left common carotid and the left subclavian arteries is narrow Coarctation of the aorta is present between the left subclavian artery and the ligamentum arteriosum.



Figure V-17 Cor triloculare biatriatum without transposition of the great vessels in a male infant aged 21 days

a Viewed from the right are the single ventricle, the common atrioventricular orifice and valve and a defect in the inferior part of the atrial septum

b The heart and great vessels from in front, showing correct relationship between the great arteries The probe extends from the pulmonary trunk through the ductus arteriosus and into the upturned descending aorta.

Abbott reported 13 examples among 1000 cases of various types of congenital cardiac malformations.

The functional effect of an absent ventricular septum is quite different from that of an uncomplicated ventricular septal defect In cor triloculare biatriatum the undivided ventricle is the common ejector for blood to both the aorta and the pulmonary trunk. The relative volume of blood flowing from this common ejectile source into each of the two great arteries will depend upon the magnitude of the resistance in the systemic vascular bed as compared with that in the pulmonary. After birth there is normally a tendency for the resistance to pulmonary blood flow to be much less than the resistance to systemic blood flow. In a given case of cor triloculare biatriatum it would be expected that a great flow of blood to the lungs would occur at the expense of systemic blood flow, if the intrapulmonary hemodynamics were similar to the normal. Under these circumstances the great pulmonary blood flow, alone or coupled with the concomitant deficient systemic blood flow, might explain death when it occurs in the early postnatal period. The patients with cor triloculare biatriatum who live through childhood probably have a regulatory mechanism which determines relative amounts of pulmonary and systemic blood flow. Such a regulatory mechanism might be sought in a state of tone of the pulmonary arteries. With reduced caliber of the pulmonary arteries, the resistance to pulmonary blood flow would be greater than normal, and might explain equal distribution between the blood which flows to the pulmonary and systemic circuits and by the same token, survival. Pulmonary hypertension would be a component of such a supposed regulatory complex (Edwards and Chamberlin, 1951).

In this connection the case of Favorite

is interesting. His patient was a young man 18 years of age who was cyanotic. The heart showed a large ventricular septal defect of such large size that the ventricles, for practical purposes, constituted a single chamber. The great arteries were transposed and the aortic opening was extremely narrow, measuring but 9 mm in diameter. The pulmonary orifice measured 4 3 cm. in diameter and the ductus arteriosus was patent. In this case it is justifiable to consider that most of the blood leaving the ventricular part of the heart left by way of the pulmonary trunk and that the ductus arteriosus carried blood to the aorta. The small aortic outlet would of course reduce the initial aortic pressure somewhat, thus facilitating some contribution to the systemic circuit from the pulmonary arterial system by way of the ductus arteriosus. To build up sufficient systemic pressure to support life for 18 years, however, there must have been in addition enough resistance to intrapulmonary flow to raise the pulmonary pressure to levels sufficient to operate this shunt effectively. It is of considerable interest that in this case death was caused by rupture of the pulmonary trunk. In this subject, we would expect to find vascular changes in the lungs similar to those in cases of coarctation of the aorta associated with patent ductus arteriosus, in which the ductus enters the aorta distal to the coarctation. In the latter condition, blood to the lower part of the body is carried from the pulmonary arterial system through the ductus arteriosus into the descending aorta (Edwards *et al*, 1949, see page 466). Unfortunately the report of Favorite does not include an extensive description of the smaller pulmonary vessels.

Survival with cor triloculare biatriatum is usually short. Among the cases collected by Abbott (1936) the age of death ranged from birth to 35 years. This series included four patients who had lived to the age of 21 years.

Cases with long survival include that of Favorite in which the patient lived to 18½ years. The patient of Drey, Strauss and Gray lived 14 years, that of Steinwinder and McPeak (1929) 23 years, that of Herndon, Vass and Donovan (1939) 49 years, and that of Mehta and Hewlett (1945) 56 years. In contrast to these examples of relatively long survival, in the Mayo Clinic series (Rogers and Edwards, 1951) of nine cases of this malformation the longest survival was eight years. Of the remaining patients two died at nine and 10 months, respectively, one at five months, and one at 2½ months, two patients at the ages of two and five weeks, respectively, and two at three years and six years, respectively. It is conceivable that the relatively long periods of survival, among the cases reported in the literature, may be explained by the greater likelihood of reporting instances with unusually long survival periods. Consequently a truer picture of the over-all survival would be obtained from reports of all cases coming under the observation of several authors rather than from reports of isolated cases.

Cor triloculare biatriatum is to be distinguished from *cor triloculare biventriculare*. The latter condition has been discussed under malformations of the atrial septal complex. In cor triloculare biventriculare the ventricular septum is intact but the atrial septum is absent or is defective to such a degree that it may be considered to be absent from a functional point of view. Consequently, hearts with cor triloculare biventriculare function essentially like those with atrial septal defects. The normal differential pressures between the ventricles are maintained. The average age at death in cases of cor triloculare biventriculare is approximately the same as in cases of atrial septal defect and

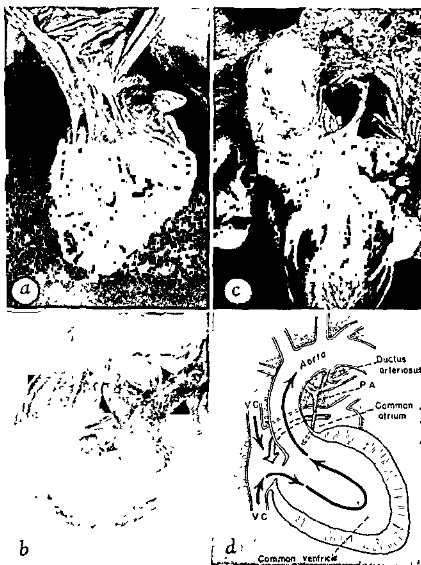


Figure V-18. Cor biloculare in a female infant eight months old. (From Edwards, J. E *Postgrad Med*, 3 327-341, 1948. Reproduced by permission of *Postgraduate Medicine*)

a The common atrium viewed from above. Immediately superior to the common atrioventricular valve is an abortive septum There is a left persistent superior vena cava which enters the left side of the common atrium.

b The common ventricle. The probe passes through the orifice of the common atrioventricular valve. A wide aorta is the only artery in communication with the common ventricle

c. The unopened heart and great vessels viewed from the left. Behind the functioning and transposed aorta lies an atretic, cordlike, pulmonary trunk

d. The intracardiac circulation and the arterial pathways to the lungs in the case of cor biloculare illustrated in *a*, *b* and *c*. *P.A*, pulmonary trunk, *V.C*, vena cava.

higher than in cases of cor triloculare biatriatum.

Cor Biloculare. Cor biloculare, characterized by absence of the atrial and ventricular septa and frequently by the presence of a common atrioventricular valve, is a malformation which functions essentially as does cor triloculare biatriatum The atrial septum may at times be represented by one of several strands of tissue but these are ineffective in acting as a septum (Figure V-18*a*). There are, as a rule, two auricular appendages Since there is no ventricular septum (Figure 18*b*), there is no differential pressure between the ejective force that supplies blood to the lungs, on one hand, and the force which delivers blood to the systemic arterial system, on the other. Consequently, as explained in the consideration of cor triloculare biatriatum, there must be a regulatory mechanism within the lungs if the blood which leaves the single ventricle is to be distributed effectively both to the lungs and to the systemic circulation Since death at an early age is common in cases of cor biloculare, there is reason to believe that such a regulatory mechanism is usually wanting. Cor biloculare is uncommon.

Abbott (1936) included only 13 cases in her analysis of 1000 cases of congenital cardiac malformations. There are two specimens of this condition among the 212 specimens of major congenital cardiovascular malformations in the Mayo Clinic pathologic collection.

It is common for cor biloculare to be associated with malformations of the great arterial vessels. For example, among Abbott's 13 cases of this cardiac anomaly there was but one case in which the aorta and the pulmonary trunk were properly interrelated. In this respect Derow's (1934) case was similar. Usually there is either an associated persistent truncus arteriosus or transposition of the great vessels. When transposition occurs, it is common for the pulmonary trunk to lie behind the aorta and to be atretic (Figure V-18*c*). In this way the aorta is the only functioning artery which leaves the heart. Under such circumstances blood is carried to the lungs by way of a patent ductus arteriosus (Figure V-18*d*)

The latter vascular arrangement was present in the cases of Lightner (1939), Rossman (1942), Miskall and Fraser (1946), Kugel (1932) and in one case in the Mayo Clinic collection. The case of Popják (1942) is essentially like these. While no pulmonary trunk was found, a patent ductus arteriosus carried blood to the lungs. As will be explained under the section on Persistent Truncus Arteriosus, such a vascular arrangement is not to be classified as persistent truncus arteriosus Instances of cor biloculare with associated persistent truncus arteriosus are reported by Goltman and Stern (1939), Giustra and Tosti (1939), and Michelson (1943)

The survival in cor biloculare is usually short. In nine of Abbott's cases the mean age at death was three years The oldest patient in that series was the patient of Rudolf (1900), a girl who lived to the age of 16 years. In recent literature, Taussig (1947) reported this malformation in a patient (Case 40) who lived 25 years. As far as I am aware, this case represents the longest survival reported for cor biloculare. Among 11 other cases the longest survival was 9½ months, in the case reported by Rossman

The term "cor biloculare" should be reserved for clear-cut examples of two-chambered hearts. In certain cases reported as cor biloculare, in which the heart functioned as though there were two chambers, there is reason to believe that hypoplastic ventricles had been overlooked. For example in a case of mitral and aortic atresia the left ventricle may be so small as

to escape detection unless microscopic sections taken from appropriate locations are studied to determine if a diminutive ventricle exists. Similarly in the hearts in which there is coexisting tricuspid and pulmonary valvular atresia, the right ventricle may be so small as to be overlooked. Probably some of the cases reported as examples of cor biloculare, in reality, represent such combinations of anomalies. The cases here quoted, however, are believed to be *bona fide* examples of cor biloculare.

Left Ventricular-Right Atrial Communications

In rare instances a membranous septal defect may create a peculiar communication between cardiac chambers. Whereas the usual communication in membranous ventricular septal defect is between the right and left ventricles, there are instances in which the left ventricle communicates, not with the right ventricle, but with the right atrium Such communications have been reviewed by Perry, Burchell and Edwards (1949) These communications may take several forms, as follows (Figure V-19): (1) The defect of the membranous *septum may be continuous with a defect in* the floor of the right atrium, as in the case of Buhl (1857) and that of McCullough and Wilbur (1944); (2) there may be an associated opening in the septal leaflet of the tricuspid valve and the edges of this opening may be fused to the right side of the margins of the ventricular septal defect. In this way intraventricular communication is prevented but the left ventricle communicates, instead, with the right atrium (Perry *et al.*). In other instances, as in the cases of Gutzeit (1922) and of Hemsath and associates (1936), the ventricular septal defect in itself is of the usual variety but the tricuspid valve is deformed. The septal deformity is such as to allow entrance of arterialized blood into the right ventricle. The valvular deformity allows regurgitation of some of the arterialized blood from the right ventricle secondarily into the right atrium.

Concerning the developmental basis for defects of the type reported by Buhl, it will be recalled that anatomically the

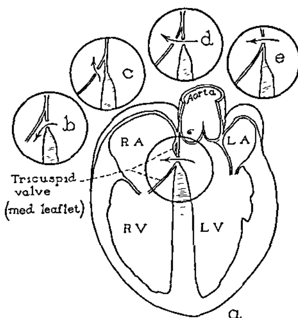


Figure V-19 Diagrammatic representation of communication between the left ventricle and the right atrium, and associated conditions

a A representation of the defect in the case of Perry and associates (1949) There is a combination *of a defect in the membranous part of the ventricular* septum and a double orifice of the tricuspid valve The adjacent edges of the two defects are fused so that the left ventricle communicates with the right atrium

b The usual type of defect involving the membranous part of the ventricular septum There is communication between the two ventricles

c. Double orifice of tricuspid valve involving the septal or medial leaflet

d. Defects in the cases reported by Gutzeit (1922) and by Hemsath and associates (1936). As in *a* there is a combination of a defect in the membranous part of the ventricular septum and double orifice of the tricuspid valve. In contrast to the conditions in *a*, the edges of the two defects are not fused

e Defects in the cases reported by Buhl (1857) and by McCullough and Wilbur (1944). In contrast to the conditions in *a* and *d*, the defect of the membranous part of the ventricular septum lies above the orifice of the tricuspid valve and is associated with a defect in the floor of the right atrium. The tricuspid valve is normal. (From Perry, E. L, Burchell, H B, and Edwards, J. E.: *Proc Staff Meet, Mayo Clin*, 24.198-206, 1949.)

membranous portion of the ventricular septum of the adult heart has a segment which lies between the floor of the right atrium and the aortic cone of the left ventricle (Figure III-22). This is the so called atrioventricular part of the membranous septum, which was formed from the right tubercles of the endocardial cushions of the atrioventricular canal and the conus septum (Figure II-25). Buhl's case represents a deficient contribution on the part of these components to the formation of the membranous septum. Though exceedingly rare, this type of membranous septal defect represents one of the types to be expected on the basis of the multiple contributions to the membranous septum, any one of which may be defective Mall in 1912 stated that the communication between the left ventricle and right atrium in Buhl's case could have been caused by secondary perforation of an aneurysm of the membranous portion of the ventricular septum. The second type (Figure V-19*a*) is probably a fortuitous combination of ventricular septal defect and so-called double orifice of the tricuspid valve.

Clinically, unusual communications as described may produce an unexpected group of manifestations. The murmur characteristic of ventricular septal defect may be present and the roentgenologic manifestations are those of an arteriovenous shunt. Should catheterization of the right atrium be performed it is expected that the blood removed from this chamber would show some degree of arterialization. Though this finding taken by itself would suggest the presence *either of an* atrial septal defect or of anomalous drainage of the pulmonary veins into the right atrium, it seems probable that the right atrial pressures would differ from those in the two *conditions just* mentioned. From a clinical study, including cardiac catheterization, it would be difficult to distinguish a communication between the left ventricle and the right atrium from the ordinary type of ventricular septal defect associated with tricuspid insufficiency.



Figure V-20 Aneurysm of the membranous portion of the ventricular septum in a patient 18 years old with mongolian idiocy who died of pulmonary tuberculosis As in the case of Rae (1936) there is some degree of subaortic stenosis beneath the aneurysm. (Photograph of specimen reproduced by permission of Dr H Milton Rogers)

Aneurysm of the Membranous Portion of the Ventricular Septum

Aneurysms of the ventricular septum involve its membranous portion. They produce no disturbances of clinical significance. They are represented by an outpouching of the membranous septum toward the right. The mouth of the aneurysm lies inferior to the aortic orifice (Figure V-20). On the right side the base of the aneurysm bulges into the right ventricle, beneath the septal leaflet of the tricuspid valve, or into the base of the right atrium just above the attachment of this leaflet (Cannell, 1930). It is evident that the presenting portion of the aneurysm on the right side involves the same locations as those involved by the right side of the opening in ventricular septal defects. Mall (1912) concluded that aneurysms of the

ventricular septum were not due to endocarditis In this he was undoubtedly correct. His emphasis of the position of the aorta abnormally far to the right, rests on less secure evidence. He believed that this, combined with the displacement of the muscular septum to the left, caused a horizontal position of the membranous portion of the septum which led to its weakness. Pending the acquisition of more accurate knowledge as to the details of the later stages in the development of the membranous septum, Mall's conclusion on this form must be regarded as merely tentative, although it seems to receive some support from a case reported by Rae (1936)

Rae's patient was a man 63 years of age, who, in addition to an aneurysm of the membranous septum, had subaortic stenosis

In the section on Defects of the Valves it is pointed out that persistence of a common atrioventricular canal is frequently accompanied by mongolian idiocy. This cardiac malformation is readily traced to improper development of the atrioventricular endocardial cushions In this connection the report of Lev and Saphir (1936) of two cases of aneurysm of the ventricular septum is interesting in that both of the patients were mongolian idiots. These cases would tend to indicate that aneurysm of the ventricular septum is associated with some basic abnormality in the development of the atrioventricular endocardial cushions. It will be recalled that these cushions play a role in the development of the pars membranacea.

Dr. H. Milton Rogers has observed a case, similar to those of Lev and Saphir, of an aneurysm of the ventricular septum in the heart of a mongolian idiot. In the latter case, as in that of Rae, there was also some degree of subaortic stenosis (Figure V-20). Zadoc-Kahn and Cousin (1925) reported a case of aneurysm of the ventricular septum and absence of the atrial septum in a man aged 31 years.

Malformations Frequently Coexisting with Defects of Membranous Portion of Ventricular Septum

In the embryo a major contribution to the formation of the membranous part of the ventricular septum is made by the conus ridges which partition the primary ventricular conus into pulmonary and aortic outlets. In order for a normal membranous septum to be formed it not only is imperative that the conus ridges develop adequately in size and extent, it is equally necessary that the conus septum should extend to the primary muscular part of the ventricular septum. In its descent the conus septum must come to lie in the same plane as the ventricular septum. Conus ridges which develop out of line with the main muscular portion of the ventricular septum fail to fuse with its crest and so inevitably leave the membranous septum incomplete. It is also evident that abnormalities in the development of ridges of the conus and of the truncus arteriosus will result in malformations of the great vessels. These latter malformations represent serious types of congenital cardiac anomalies, of which patency of the ventricular septum is but a single component. For this reason those cases in which defects of the membranous part of the ventricular septum are associated with major abnormalities of the ascending aorta and of the pulmonary trunk may more logically be discussed under malformations resulting from abnormal partitioning of the truncus arteriosus and conus arteriosus. These will be described in the next section.

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Congenital Malformations

C. Malformations Resulting from Abnormalities in Partitioning of the Truncus and Conus Arteriosus

THE TETRALOGY OF FALLOT

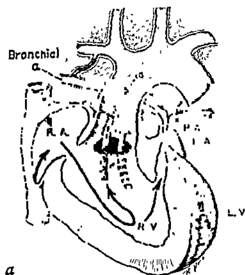
Historic and Pathologic Aspects

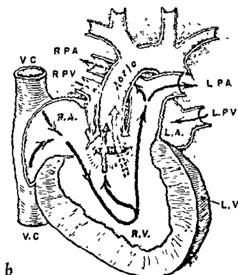
The tetralogy of Fallot is characterized by (1) origin of the aorta entirely or in part from the right ventricle, (2) a membranous ventricular septal defect; (3) pulmonary or subpulmonary stenosis, and (4) right ventricular hypertrophy (Plate V-1*a*). It is the most common type of congenital cardiac malformation characterized by cyanosis which is compatible with survival beyond the age of two years.

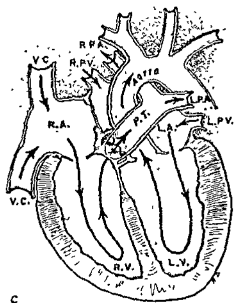
The contribution of Fallot (1888) on the clinicopathologic correlations of this condition led to his name being given to the condition. The pathologic features, however, had been described much earlier According to Bennett (1946), Sandifort in 1777 was the first to give a clear description of the condition now known as the tetralogy of Fallot.

Willius (1948) reviewed accounts of this condition which were published during the eighteenth century and the early part of the nineteenth century, including the accounts of William Hunter, Farre and Gintrac.

The writings of Meyer (1857), Stolker (1864), Peacock (1866, 1881), Kussmaul (1866), von Rokitansky (1875) and Rauchfuss (1878) contain clear descriptions of the complex. It is evident from







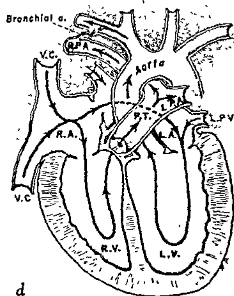


Plate V-1
a. Tetralogy of Fallot
b. Eisenmenger complex

c. Isolated pulmonary stenosis with closed atrial septum
d. Isolated pulmonary stenosis with patent foramen ovale.

the reviews of Keith (1909), Herxheimer (1909) and Poynter (1919), from Brown's excellent monograph (1939) and from Bauer and Astbury's (1944) bibliography of the 1000 cases of congenital cardiac disease analyzed in Maude Abbott's *Atlas* that many contributed to the knowledge of the pathologic features of this condition during the second half of the nineteenth century

The structural variations among specimens with the tetralogy of Fallot may be considered at this point.

The Heart. The main differences between various examples of the tetralogy of Fallot depend largely on (a) the anatomic cause for the barrier to pulmonary blood flow and (b) the connection of the aorta with the heart.

The barrier to pulmonary blood flow will be considered first. *Pulmonary atresia* is less common than pulmonary stenosis In 1909 Herxheimer collected from the literature data on 597 cases of pulmonary stenosis or atresia and estimated that the total number of such cases reported up to that time was about 700. Evidently this collection constituted all types of pulmonary stenosis or atresia. Since the tetralogy of Fallot is by far the most common malformation in which pulmonary stenosis or atresia is present, it seems valid to use Herxheimer's figures as an index concerning the incidence of pulmonary stenosis as compared with atresia in this malformation. Of an estimated 700 cases of pulmonary stenosis or atresia in the literature, he believed that from 550 to 580 would be examples of pulmonary stenosis and only 100 to 120 would have pulmonary atresia. This would give a ratio of about five cases with pulmonary stenosis to one with pulmonary atresia. This ratio conforms with my own experience. Pulmonary atresia may take one of several forms.

As in the cases of Greenspon and Leaman (1939) and of Miskall (1945), the entire pulmonary trunk may be closed and narrow, resembling a fibrous cord. In other instances the lower part of the trunk is atretic, the upper part of the trunk being patent though narrower than normal (Figure V-21*a*) (East and Barnard, Case 1, 1938, Sternberg and associates, 1947). In the latter two cases no pulmonary valvular tissue was identified. In other cases (Read and Krumbhaar, Case 2, 1932; Hemsath and associates, Case 2, 1936) the pulmonary trunk was closed off from the right ventricle by a membrane which represented fusion of the pulmonary valvular leaflets (Figure V-21*b*). The third case of Abbott, Lewis and Beattie (1923) showed yet another form of pulmonary atresia. In that case the right ventricular subpulmonary tract was closed just below the level of the pulmonary valve which was represented by three rudimentary cusps

Cases of the tetralogy of Fallot with atresia of the lower portion of the pulmonary trunk have been called "truncus arteriosus" by Taussig (1947a, b). In 1949 Cooley and associates referred to this type of the malformation as "pseudotruncus arteriosus" and indicated that in so doing they adopted Dr. Taussig's more recent designation. It is, however, appropriate from a developmental point of view to avoid the term "truncus arteriosus" in this condition. Though the pulmonary trunk is atretic and the aorta the only functioning one of the two great arteries, the presence of an aorta and of a pulmonary trunk, regardless of the size of their lumina, is sufficient evidence that the truncus arteriosus had been partitioned.

In the usual instance, when any one of the forms of pulmonary atresia exists, the left and right pulmonary arteries are present and patent. In circumstances of pulmonary atresia, no blood flows through

normal channels to the lungs If life is to be maintained some collateral channels *must* be present. In most of the cases the ductus arteriosus plays this role during the first two weeks *after birth. Usually*, however, despite the desirability of *continued* patency of the ductus arteriosus, it closes as in normal persons.

In a case of Abbott, Lewis and Beattie (Case 3), that of a boy aged 11 years with pulmonary atresia, and in Miskall's *patient who was 2½ years old, the* ductus arteriosus remained patent. In other instances of pulmonary atresia the ductus was found closed. The bronchial arteries *were prominently dilated and undoubtedly* were responsible for providing life-preserving blood flow to the lungs. Examples of such cases are those of East *and Barnard (patient No. 1, aged 33 years)*; Greenspon and Leaman (patient aged 5 years); and Sternberg and associates (1947, patient aged 3½ years) In *Taussig's case (1947b, Case 1), that of an* infant four months of age, the lower part of the pulmonary trunk was atretic and *there was* no identifiable vestige of a *ductus arteriosus. The bronchial arteries* were wide and represented the channels through which blood was carried to the lungs.

The frequent occurrence of death in the early postnatal period in cases of pulmonary atresia *is* probably explained by closure of the ductus arteriosus at an early date and at a *time before the bronchial* arteries have become sufficiently enlarged to carry blood to the lungs in amounts adequate to maintain life.

Often, in *the tetralogy of Fallot there* is no closure of the arterial channels leading to the lungs but there is sufficient *pulmonary stenosis* at one region or another to cause a significant *barrier to* pulmonary blood flow.

In unusual instances, as in those of Chase (1929) *and* of *Feldman* and Snook (1938) the pulmonary trunk, though patent, *is so narrow as* to constitute the important barrier to pulmonary blood flow. Usually, however, the pulmonary trunk, though often narrower than normal, is not *the site of the* significant stenosis. It usually would be wide enough to carry adequate amounts of blood to the lungs were there no stenosis either *at the level* of the pulmonary valve, or lower, in the *subpulmonary region of the right ventricle* While the pulmonary trunk is usually narrower than the aorta and narrower than normal (Figure V-21*c*), *at times it is of normal width or wider than normal* (*White* and Boyes, 1932) (Figure V-21*d*) *This* feature may cause, in the *roentgenogram*, unusual prominence of the *pulmonary arterial shadow in the tetralogy of Fallot* (Dry *et al*, 1948, Baker *et al.*, 1949)

Stenosis of the orifice of the *pulmonary* valve is commoner than stenosis of the *lumen of the pulmonary trunk. The pul*monary valve is often bicuspid (Figure V-22*a*; Koletsky, 1941). In some instances, particularly when the valve is bicuspid, it *may be so constructed as to cause stenosis* (Edwards *et al.*, 1947). Under these conditions the two cusps are fused, converting the valvular tissue into a cone-shaped *structure with a narrow lumen at its apex* (Figure V-22*b*). The cone projects upward into the pulmonary trunk

In some cases the pulmonary valve constitutes *the site of the greatest barrier to* pulmonary blood flow, as in the following cases with bicuspid pulmonary valve: Moore (1885), Black (1914) and Roth*stadt (1939). In the case of* Leader and Kugel (1934) valvular stenosis was caused by fusion of three pulmonary cusps. White and Boyes (1932) have suggested that the *bicuspid pulmonary valve in the tetralogy* of Fallot may allow regurgitation.

In some instances the barrier to



Figure V-21. Tetralogy of Fallot.

a Pulmonary trunk and right ventricle showing atresia of inferior portion of pulmonary trunk There was no connection between the cavity of the right ventricle and the pulmonary trunk in serial sections, one of which is here illustrated *P T*, indicates pulmonary trunk, *V S D*, ventricular septal defect, *C S*, crista supraventricularis, *R V*, outflow tract of right ventricle Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, X 4. (From a specimen of heart of an infant aged 11 weeks, submitted by Dr. Frederic Parker, Jr, Mallory Institute of Pathology, Boston, Massachusetts)

b The pulmonary trunk and pulmonary valve from a woman aged 23 years The pulmonary trunk has been opened, exposing an atretic bicuspid pulmonary valve which projects as a cone into the lumen of the pulmonary trunk

c. The aorta and pulmonary trunk have been divided immediately above the semilunar valves The pulmonary trunk is narrower than normal and considerably narrower than the somewhat dilated ascending aorta. The pulmonary valve has three cusps, an arrangement which is relatively unusual in the tetralogy of Fallot From a girl seven years of age Other illustrations from this case are found in Figures V-25*b* and *c*, and V-26*a* and *b*

d The heart, great vessels and lungs from a case of the tetralogy of Fallot in which the pulmonary trunk is of normal width. From a boy 13 years of age. A photomicrograph from the wall of the stenotic subpulmonary tract which caused the barrier to pulmonary blood flow is illustrated in Figure V-25*a*.



Figure V-22 Tetralogy of Fallot

a. The aorta and pulmonary trunk have been cut across above the semilunar valves Notice the bicuspid pulmonary valve, this caused no appreciable stenosis in this case From a boy two years of age

b The open pulmonary trunk and subpulmonary outflow tract of the right ventricle contain the probe The pulmonary valve, which hides part of the probe, is bicuspid and its orifice is stenotic From a girl 14 years of age

c The right ventricle and aorta The outflow tract of the right ventricle, which lies between the crista supraventricularis (*C S*) and the ventral wall of the right ventricle (*R V.*), is a cylindrical channel, not particularly narrow A bicuspid pulmonary valve was responsible for the barrier to pulmonary blood flow in this case From a boy five years of age (From Dry and associates, 1948 Reproduced by permission of the authors and *Postgraduate Medicine*)

pulmonary blood flow seems to be a combination of valvular stenosis and a narrow condition of the subpulmonary outflow tract of the right ventricle (Liboro and Hilario, 1933)

The commonest cause for impairment to pulmonary blood flow in the tetralogy of Fallot is the narrow state of the subpulmonary outflow tract of the right ventricle, as observed by Meyer (1857), Stolker (1864), Kussmaul (1866), von Rokitansky (1875), Peacock (1881), Abbott (1927), Bach (1928), Harrison (1929), Brock (1949) and many others

The *anatomic nature of the subpulmonary tract* will next be considered. The tract is bounded anteriorly by the ventral wall of the right ventricle, on the left by the ventricular septum, and posteriorly by a mass of muscle which separates the tract from the ventricular septal defect The exact nature of this mass of muscle is not clear, but probably it is an enlarged crista supraventricularis. Since there is a trend toward surgical attack directly on the pulmonary stenosis of the tetralogy of Fallot (Brock, 1948 and 1949) by operating on the subpulmonary tract or by approaching the stenotic valve through the tract, it is important to recognize the various forms that the subpulmonary tract may take At times, it is merely a cylindrical channel and not particularly narrow (Figure V-22*c*). More commonly, however, the tract is significantly narrow. Though the tract may be relatively straight

course, it usually has a sigmoidal shape (Figure V-23*a*, *b* and *c*). The latter is brought about to a great extent by the prominence of the lower portion of the mass of muscle which forms the posterior wall of the subpulmonary tract. The subpulmonary tract is often of irregular diameter. The opening between the main part of the right ventricle and the tract represents the narrowest part of the tract in many cases (Figure V-24*a* and *b*).

Endocardial thickening of the tract, as in the case of Segall (1933), is the result of formation of collagen and elastic tissue (Figure V-25*a*) and adds to the irregularity of the contour of the channel. These deposits may represent reactions to the trauma of eddies in the blood which flows from the right ventricle into this tract. At times there may be warty vegetations deposited in irregular locations on the wall of the subpulmonary tract (Figure V-23*b*) These are largely composed of fibrin and platelets and also may result from trauma, possibly the thickened endocardium in part represents organization of such vegetations deposited at earlier periods. Brock (1949) has emphasized that the secondary changes in the lining of the subpulmonary tract make the channel more rigid and progressively more stenotic.

In rare circumstances either the left or the right pulmonary artery is absent. Blalock (1948) observed at operation or necropsy that one of the pulmonary arteries was absent in nine of 610 patients operated on for pulmonary stenosis.

The Aorta. The aorta usually arises from each ventricle above the ventricular septal defect. In an exceptional instance the aorta arises exclusively from the right ventricle. When this happens the only outlet



Figure V-23. Tetralogy of Fallot

a The right ventricle and aorta have been opened, revealing the *characteristic features* of the tetralogy of Fallot The sigmoidal subpulmonary outflow tract of the right ventricle is shown lying between the crista supraventricularis (*C.S.*) and the ventral wall of the right ventricle (*R.V.*). From a boy six years of age The open pulmonary trunk and pulmonary valve are shown in *b*

b. The subpulmonary outflow tract of the right ventricle and the opened pulmonary valve and trunk The thick endocardium of the subpulmonary tract of the right ventricle is evident. The tract lies between the crista supraventricularis (*C S*) and the ventral wall of the right ventricle (*R.V.*). In the inferior part of the tract, warty vegetations are attached to the endocardial wall. The pulmonary valve is bicuspid

c. The outflow tract of the right ventricle and the open pulmonary trunk in the case of tetralogy of Fallot also illustrated in Figure V-21*b*. The outflow tract of the right ventricle lying between the crista supraventricularis (*C S.*) and the ventral wall of the *right ventricle* (*R V.*) *is narrow* and has a *sigmoidal* shape brought about by the projection of the crista supraventricularis into the channel.

for the left ventricle is the ventricular septal defect. Origin of the aorta from the right ventricle should not exclude a case from being classified as an example of the tetralogy of Fallot if the other features of the complex are present. One potential peculiarity of this type of case is that in the presence of a small ventricular septal defect a barrier may exist to emptying of the left ventricle Taussig (1948) has emphasized that in this structural arrangement, if the septal defect is small, pulmonary congestion may complicate an anastomotic operation performed for pulmonary stenosis (Blalock and Taussig, 1945; Potts, Smith and Gibson, 1946)



Figure V-24 Tetralogy of Fallot in a boy three years of age

a The aorta is in free communication with the right ventricle as well as with the left above a ventricular septal defect The subpulmonary tract of the right ventricle has a very narrow inlet lying between the prominent crista supraventricularis (*C S.*) and the ventral wall of the right ventricle (*R V*) A close-up view of this tract is shown in *b*

b Opened subpulmonary tract showing the narrow inlet lying between the crista supraventricularis (*C S*) and the ventral wall of the right ventricle (*R V*). Above the narrow inlet the subpulmonary tract widens materially, as does the pulmonary trunk The pulmonary valve has three cusps.

Reported examples of the tetralogy of Fallot in which the aorta arose entirely from the right ventricle include those of Meyer (1857), Weiss (1875), Heller and Gruber (1914), Feldman and Snook (1938), Volini and Flaxman (1938), Talbott and associates (1941), Hardgrove and Gramling (1944), and Brodie (1945).

The *aortic valve* in the usual case of the tetralogy of Fallot is normal, having three well-formed cusps. In rare instances, though three cusps are present, they are of unequal size At other times there are four cusps, three of which are essentially normal, the fourth being rudimentary The histologic structure of the aortic wall is normal (Figure V-25*b*), in contrast to the condition of the wall of the pulmonary trunk (Figure V-25*c*) which is thinner than normal The thickness of the pulmonary trunk is often compared to that of a vein, histologically the media is thin and its elastic fibers are often represented as discontinuous strands

The *coronary arteries* arise from the aorta and frequently their ostia are located in an anomalous position with respect to the aortic sinuses Occasionally, one coronary artery may be absent.

In Bach's case (1928) only the right coronary artery was present. In one specimen which the author has observed, the ostium of the left coronary artery was stenotic, though the vessel beyond thi

point was of normal caliber; the right coronary artery was normal. In this case the wall of the left ventricle showed wide areas of scarring resembling healed infarct.

A cardinal feature of the tetralogy of Fallot is that the thickness of the *right ventricular wall* is greater than normal, and usually equals or exceeds that of the left ventricle. This is understandable since the right ventricle shares with the left the function of supplying blood to the aorta. In this respect, the right ventricle of a patient with the tetralogy of Fallot resembles that of the normal fetus in that the right ventricle and the left each acts as a systemic ventricle. Patten (1946) has emphasized that the thick right ventricular wall in the tetralogy of Fallot, therefore, represents a persistence of a fetal relationship between the two ventricles. The *chamber of the right ventricle* may be of normal size, but often it is somewhat larger than that of the left ventricle. This enlargement is explained by the greater return of blood through the systemic veins to the right side of the heart than of blood through the pulmonary veins to the left side of the heart. The enlarged and thickened right ventricle characteristically forms the cardiac apex (Pescatore *et al.*, 1939).

The report of Gasul and associates (1949) was exceptional. Their patient was a girl aged nine years whose heart showed an associated atrial septal defect and enlargement of the left ventricle; electrocardiographic left axis deviation was dem-



Figure V-25. Tetralogy of Fallot. Photomicrographs from two cases of tetralogy of Fallot prepared from sections stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain.

a. The endocardium of the outflow tract of the right ventricle is greatly thickened by collagen and elastic tissue X 20 The heart and lungs in this case were illustrated in Figure V-21*d*.

b The aorta, showing normal structure contrasted with the pulmonary trunk illustrated in *c*. X 30

c. The pulmonary trunk, showing a thin media and irregular distribution of elastic tissue. The gross specimen from which *b* and *c* were prepared is illustrated in Figure V-21*c*.

onstrated during life. Cooley and associates (1949) reported that in a boy aged three years and eight months the clinical and angiocardiographic findings were consistent with the tetralogy of Fallot, except for the electrocardiographic features which showed left axis deviation and suggested a left ventricular predominance. In a case of Taussig (1947b) the left ventricle was larger than the right.

The foramen ovale often shows *probe-patency*. Abbott (1927) reported that of 73 cases of the tetralogy of Fallot characterized by pulmonary stenosis the foramen ovale was patent in 29 instances. Among 24 cases with pulmonary atresia the foramen was patent in 14 cases. While probe-patency is common, a true patency of the atrial septum is uncommon.

The Pattern of the Aortic Arch. The usual case shows the aortic arch and descending aorta in normal locations. In about one-fifth to one-fourth of the cases, however, the aortic arch is on the right side, arching over the root of the right lung. The association of a right aortic arch with the tetralogy of Fallot is at times referred to as *Corvisart's disease* (Corvisart, 1818).

In 1948 Blalock and Bahnson reported that in approximately 140 of 610 patients operated upon for congenital pulmonary stenosis, most of whom had the tetralogy of Fallot, a right aortic arch was present. Dammann, Gibson and Potts (1949) found a right aortic arch in 28 (26 per cent) of 108 patients operated upon for cyanotic congenital cardiac disease Baker and associates (1949) reported 14 instances of right aortic arch among 50 patients operated upon for pulmonary stenosis. The great majority of the 50 subjects had the tetralogy of Fallot

When a right arch is present, the upper portion of the descending aorta is usually likewise on the right side (Figure V-26*a* and *b*). In the lower part of the thorax, at about the level of the eighth thoracic vertebral body, the aorta then deviates to the left and leaves the thorax through the aortic hiatus of the diaphragm (Edwards, 1948). When the aortic arch is on the right side, the branches of the arch are usually reversed (Figure V-26*c*). The first branch is an innominate artery, from which the left common carotid and left subclavian arteries arise; the second branch of the arch is the right common carotid artery, and the third, the right subclavian artery. Variations in this pattern exist, the more common of these probably being one in which four branches arise directly from the right aortic arch. Under these conditions the first is the left common carotid artery, the second, the right common carotid; the third, the right subclavian artery; and the fourth, the left subclavian artery. In this respect, the aortic arch and its branches form a mirrored image of that common malformation in which the right subclavian artery arises as the fourth branch of an otherwise normal aorta (See section on Malformations of the Aortic Arches.)

When the left subclavian artery arises as the fourth branch of the right-sided aorta, it passes behind the esophagus to reach the left arm. In this instance, the anomalous subclavian artery may compress the esophagus and at times may be responsible for dysphagia, its presence may be detected on roentgenography.

While the upper portion of the descending aorta is usually on the right when the aortic arch is on the right, in a relatively small number of cases the right arch crosses the midline behind the esophagus to join the upper portion of the descending aorta on the left side of the thorax.

Double aortic arches may be present occasionally. Blalock and Bahnson found one example of this aortic malformation in the 610 which they reported. Harris and Whitney (1927) encountered this malfor-

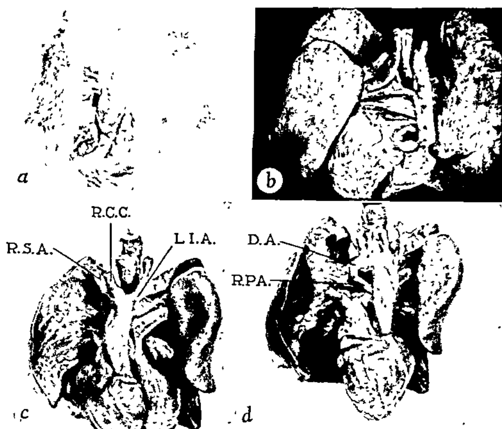


Figure V-26 Tetralogy of Fallot with right aortic arch.
a The arch of the aorta passes ventral to the root of the right lung
b Posterior view of the thoracic organs After the arch of the aorta has passed ventral to the root of the right lung, the upper part of the descending aorta remains on the right (Figures *a* and *b* were prepared from a girl seven years of age.)
c The aortic arch is on the right side Its branches are reversed compared to normal The first branch is the left innominate artery (*L I A.*), the second is the right common carotid (*R C C*), and the third, the right subclavian artery (*R S A.*)
d The arch is viewed from the right side. The ductus arteriosus (*D A.*) runs between the right pulmonary artery (*R P A.*) and the aortic arch (Figures *c* and *d* were prepared from a female infant 22 days old)

mation in a peculiar form. The right of the two aortic arches was by far the wider of the two. In spite of a left-sided ductus arteriosus the upper portion of the descending aorta was on the right side of the body. Paul (1948) described the condition of a left aortic arch with a right descending aorta in two cases in which operation was performed for the tetralogy of Fallot.

The Ductus Arteriosus. When the aortic arch is on the left side the ductus arteriosus also is almost always on that side. When the aortic arch is on the right side, the ductus arteriosus may take one of two positions. It may run between the right pulmonary artery and the aortic arch, inserting into the arch just beyond the origin of the right subclavian artery (Figure V-26*d*). At other times, while the aortic arch is on the right, the ductus arteriosus extends from the left pulmonary artery either to the left subclavian artery (Meyer, 1857; Hemsath *et al.*, Case 2, 1936) or to the left-sided innominate artery. Blalock and Bahnson (1948) found that when there was a right aortic arch in association with the tetralogy of Fallot, the ductus arteriosus was usually a left-sided structure inserting into either the left



Figure V-27 A dorsal view of the trachea and lungs in a case of tetralogy of Fallot in which the patient was a boy six years of age Running along each bronchus is a prominent bronchial artery Other illustrations from this case appear in Figure V-23a and b (From Dry and associates, 1948 Reproduced by permission of the authors and *Postgraduate Medicine*)

subclavian or the left innominate artery (Figure V-93*c, d*).

Case 3 of Dexter and associates (1947) is of interest. The patient was a boy aged 10 years with the tetralogy of Fallot in whom clinical and catheterization studies revealed evidence of a right aortic arch associated with a right-sided descending aorta and a patent ductus arteriosus The location of the murmur of the patent ductus was unusual in that it was more prominent over the aortic area than over the pulmonary. This feature would be consistent with the ductus entering the right pulmonary artery rather than the left. The latter position, however, was represented diagrammatically in their paper.

The occasional *absence of the ductus arteriosus* is understandable Inasmuch as the aorta, during fetal life, is in free communication with the right ventricle, the ductus may be used little as a channel for bringing blood from the right side of the heart to the aorta It may atrophy during fetal life and so be unidentifiable at the time of birth.

The writer has observed one such case in which the aortic arch and upper portion of the descending aorta were on the right An identical case was described by Myers and Keith (1926) Taussig (1947b) reported an instance in which there was atresia of the lower portion of the pulmonary trunk in which no tissue of the ductus arteriosus could be found at necropsy Several instances of absence of the ductus arteriosus are listed in the review of Stolker (1864) on pulmonary stenosis

Patency of the ductus arteriosus (Miskall, 1945; Dexter *et al*, 1947) occurs but is uncommon When a patent ductus is present, it acts as an important collateral channel for blood to flow from the aorta to the pulmonary arterial system. In most patients with the tetralogy of Fallot who live to childhood or adult life, there is another well-developed system of collateral vessels, chiefly the bronchial arteries.

The Bronchial Arteries. The importance of the *bronchial arteries* as collateral pathways to the lungs (Figure V-27) in pulmonary stenosis or atresia has been rea

ized and commented on by many, including Meyer (1857), Weiss (1875), Middendorp (1886), Harrison (1929), Greenspon and Leaman (1939), Talbott and associates (1941) and others. In 1917 Christeller made an excellent review of the subject. The most graphic demonstration of the rich collateral supply to the lungs by the bronchial and other mediastinal arteries was presented by Hales and Liebow (1948). By means of vinylite corrosion casts of the lungs in five cases of the tetralogy of Fallot they demonstrated that in four of these there were gross anastomoses between the bronchial and the pulmonary arteries. It is to be emphasized that in the usual case of the tetralogy of Fallot with pulmonary atresia the collateral vessels are the sole channels by which blood comes to the lungs Moreover in many cases with severe pulmonary or subpulmonary stenosis the collateral vessels may carry more blood to the lungs than flows through the normal pathway The dilated bronchial arteries may distort the esophagus (Taussig, 1947b). This feature may be visualized roentgenographically (Cooley and associates, 1949).

The Intrapulmonary Arteries. The structure of the walls of the smaller *intrapulmonary arteries and arterioles* is within the limits of normal No thickening of the vascular walls occurs as in the Eisenmenger complex. Rich (1948) has reported on the high incidence of thrombi within the intrapulmonary arterioles in the tetralogy of Fallot. He found these of varying ages, including completely organized thrombi. Hales and Liebow (1948) have confirmed these observations. The basis for the development of a pulmonary arteriolar thrombus is not clearly evident, though it may result from polycythemia. The possibility of emboli from vegetation occurring in the outflow tract of the right ventricle must also be considered.

Functional Disturbances in the Tetralogy of Fallot

The essential functional disturbances of the tetralogy of Fallot have long been understood from studies of the clinical features coupled with correlation of the morphologic features (Fallot, 1888, Young, 1907). Early studies on the functional nature of the malformation aided in a broader understanding of the condition. Investigation of many cases of the tetralogy of Fallot by means of cardiac catheterization, by studies of peripheral oxygen saturation under varying conditions, and by angiocardiographic studies (Grishman *et al.*, 1941; Sussman *et al.*, 1943; Keith, 1948; Cooley *et al.*, 1949; Campbell and Hills, 1950) has given broader understanding of the deviations from normal which may be exhibited by patients with this disease. The value of these newer technics has gone further, yielding a more comprehensive understanding of the functional disturbances. Means of greater accuracy in diagnosis have been made available. These newer methods of study have aided in the selection of patients for surgical treatment and have made possible objective studies on the effects of operations for the malformation.

An essential feature of the tetralogy of Fallot is that the right ventricle supplies blood to the aorta and to the lungs. Since the systemic systolic blood pressure is within normal limits (Baker *et al.*, 1949), the right ventricle, which shares with the left ventricle the function of supplying blood to the aorta, must exert systemic pressure. This resembles the condition in the normal fetus, in which the right ventricle shares with the left the function of supplying blood to the systemic circulation. In the fetus the right ventricular wall is similar in thickness to the left. This is explained by the fact that the two ventricles exert similar pressures (Hamil-

ton *et al.*, 1950). In the patient with the *tetralogy of Fallot* the thick right ventricle is explained in a similar manner (Patten, 1946). Catheterization studies have demonstrated right ventricular hypertension. Moreover, simultaneous readings show that the systolic pressure of this chamber is like that in the aorta (Dexter *et al.*, 1947; Bing *et al.*, 1947). When the heart with the tetralogy of Fallot is characterized by pulmonary atresia none of the right ventricular blood flows to the pulmonary trunk. Under such circumstances the lungs depend on the collateral arteries for their blood supply. When this happens the pressure within the major pulmonary arteries is understandably low Similarly when pulmonary or subpulmonary stenosis exists the pulmonary arterial pressure is low. This is so in spite of the fact that the propelling ventricle exhibits systolic hypertension (Lagerlöf *et al*, 1949). The reason for the characteristic difference between the right ventricular pressure and that of the pulmonary trunk is explained by the interposition of the zone of stenosis.

Dow and associates (1950) reported that, in patients with the tetralogy of Fallot, studies of pressure-tracings suggested stenosis both of a valvular orifice and of the lower opening of the subpulmonary tract The basis for this interpretation was that the systolic pressure in the outflow tract of the right ventricle was greater than that in the pulmonary trunk and less than that in the main portion of the right ventricle

The volume of pulmonary blood flow is less than normal. This accounts for the characteristic "clear" roentgenologic appearance of the lungs

Bing and associates (1947) observed that in young patients the values for pulmonary capillary flow usually agreed with the values for pulmonary arterial flow. In the majority of older patients, however, the pulmonary capillary flow far exceeded the pulmonary arterial flow. The discrepancy seen particularly in the older patients was explained by flow through collateral channels such as the bronchial arteries. These investigators did not, however, find a linear relationship between age and magnitude of collateral circulation In a general way, however, it may be concluded that there is a progressive increase in collateral circulation to the lungs in patients who have the tetralogy of Fallot. This does not mean that collaterals fail to develop at an early age, even before birth

In Case 1 of Taussig (1947b), that of an infant aged four months with pulmonary atresia, the bronchial arteries were greatly dilated At necropsy it was demonstrated that the ductus arteriosus was absent. This would suggest that collaterals had developed during fetal life They were the only avenues for the passage of blood to the lungs and must have been in effective operation when at birth the umbilical cord was divided Otherwise life would have failed at that time.

The *basis for cyanosis* in the tetralogy has been discussed by Burchell (1947), Campbell (1948) and others. It is dependent in a large measure on two closely interrelated factors: (1) a shunt of venous blood from the right ventricle into the aorta, and (2) diminished pulmonary blood flow In general the greater the degree of pulmonary stenosis, the more blood will flow from the right ventricle into the aorta At the same time it is to be realized that the blood which flows from the left ventricle into the aorta is blood which has passed through the lungs, having entered the lungs through the pulmonary trunk and through the collateral channels.

If it is assumed that no collateral blood flows to the lungs, then all of the blood that leaves the left ventricle would of necessity ultimately come from the pul-

ionary trunk. This would mean that the naller the flow of right ventricular blood ɔ the lungs, the greater would be the ow of venous blood to the aorta. Under iese conditions, the greater the degree f pulmonary stenosis, the greater would e the degree of desaturation of the sysemic arterial blood and the more severe ould the cyanosis (Brock, 1949) tend to e. These rigid hypothetical conditions are robably never exactly duplicated in life. 'actors which vary in this situation are colateral flow to the lungs and changing esistances to pulmonary and to systemic lood flows Thus when severe pulmonary enosis or even atresia exists, the collateral upply may be adequate to prevent potenally profound degrees of desaturation of ne systemic arterial blood. The degree of yanosis, therefore, need not be directly orrelated with the degree of gross pullonary stenosis.

The gross barrier to pulmonary blood ow is fixed at a given time. All other actors being equal, the amount of blood hich will flow to the lungs through the rea of pulmonary stenosis will depend ithin certain limits on the level of the esistance to systemic blood flow.

In studying patients with the tetralogy f Fallot, Burchell and Wood (1949) demnstrated precipitous decreases in the oxyen saturation of the peripheral arterial lood when profound drops in systemic lood pressure occurred. A similar obseration was made by Hamilton and assocites (1950). It is to be emphasized that hese reactions probably depend on great egrees of alteration of the resistance to ystemic flow. With the levels of changes n systemic blood pressure induced by dministration of tetra-ethyl-ammonium on and phenylephrine hydrochloride Neosynephrine hydrochloride), Burchell nd Wood observed no significant change n the oxygen saturation of the arterial lood in a patient with the tetralogy of Fallot. Moreover they failed to cause a decrease in oxygen saturation of the arterial blood by applying positive-pressure breathing, a procedure which might be expected to raise the resistance to pulmonary blood flow.

Fainting spells associated with intensification of cyanosis are common in patients who have the tetralogy of Fallot. These attacks are related to increased magnitude of the venous arterial shunt (Burchell *et al.*, 1950).

During exercise, patients who have the tetralogy of Fallot characteristically show intensification of cyanosis and a fall in the oxygen saturation of the peripheral arterial blood (Rutledge and Adams, 1947; Montgomery *et al.*, 1948). This phenomenon is probably dependent on several factors, including increased oxygen uptake by the tissues, increased cardiac output decreased resistance to systemic flow and possibly increased resistance to pulmonary blood flow (Burchell *et al.*, 1950).

Survival and Complications in Tetralogy of Fallot

Survival. Length of life among patients who have the tetralogy of Fallot varies considerably.

In 1927 Abbott reviewed 97 cases of this condition, 73 of which had pulmonary stenosis. In this group the highest age at the time of death was 28 years, the average for the group with stenosis being 10.8 years In the group of 24 cases with pulmonary atresia the length of life was shorter, the average being 3.4 years and the highest age 13 years.

The characteristic shorter survival in patients with atresia as compared with those exhibiting pulmonary stenosis is probably related to the generalization that the collateral supply to the lungs is less marked in the younger patients than in the older. In the patients with atresia, a patent ductus arteriosus may be an impor-

tant collateral channel during the first few weeks after birth. When the ductus closes, the other collaterals may supply blood to the lungs in amounts insufficient to maintain life In those patients who have pulmonary stenosis the existing arterial channel to the lungs, though narrow, may be adequate to maintain life until such time as the collaterals develop to carry significant amounts of blood to the lungs.

The following authors have reported examples of patients (and their ages) with the tetralogy of Fallot who survived for unusually long periods White and Sprague (1929), 59 years, Feigin and Rosenthal (1943), 53 and 43 years, respectively, Middleton and Ritchie (1947), 45 years, Volini and Flaxman (1938), 41 years, Middendorp (1886), 33 years, East and Barnard (1938), 33 years, Perlman and Meyer (1945), 32 years, and Bach (1928), 30 years.

Complications. The *causes of death* include congestive cardiac failure, pneumonia, subacute bacterial endocarditis (Abbott, 1925), cerebral thrombosis and cerebral abscess While in some of the cases, one of these conditions may be evident at necropsy, there are others in which the cause of death cannot be demonstrated anatomically (Ash and Harshaw, 1939) Some of the patients, particularly children, may die during one of the characteristic attacks of intensified cyanosis and unconsciousness. In such cases it may be supposed that the immediate cause of death is *cerebral anoxia*. The complication of *pneumonia* is serious for two reasons for the patient with the tetralogy of Fallot Even small degrees of reduction of functioning pulmonary parenchyma may be responsible for increased hypoxia. The other factor which may be associated is peripheral vasodilatation The accompanying decreased resistance to systemic flow would tend to increase the shunt of venous blood from the right ventricle to the aorta The importance of the latter factor is unsettled, however.

Congestive cardiac failure may complicate the course of the patients who survive well into adult life (Feigin and Rosenthal, 1943, Middleton and Ritchie, 1947) It does not seem to be a prominent cause of death among those who die during childhood or adolescence.

Bacterial endocarditis is a complication of some consequence, particularly in those patients who survive childhood Among the 97 cases of the tetralogy of Fallot which Abbott (1927) reviewed, bacterial endocarditis was present in 18 of the 73 patients with pulmonary stenosis but in none of the 24 with pulmonary atresia. The difference in incidence of bacterial endocarditis between the two groups is probably best explained by death at an early age from other causes in the patients with pulmonary atresia. Since bacterial endocarditis represents a fortuitous complication in a fertile field, the shorter the life, the less the likelihood of bacteremia. Conversely, the longer the patient lives the greater the likelihood of bacteremia and so the greater his chances of developing this complication

Gelfman and Levine (1942) observed that bacterial endocarditis was a complication in 12 5 per cent of patients, of all ages, with the tetralogy of Fallot Among only those patients who were two years of age or more, a complicating bacterial endocarditis was found in 29 per cent.

The endocarditis usually involves the right side In the cases reported by Harrison (1929), White and Boyes (1932) and Perlman and Meyer (1945) the infection appeared to have started on the tricuspid valve. In the patient of Dustin and Lambert (1942) the infection originated on the wall of the subpulmonary outflow tract of the right ventricle, and in Leadingham's (1930) patient the pulmonary valve

the site of bacterial endocarditis. In each of the cases cited the patient was 15 years of age or older at the time of death.

Cerebral thrombosis as a complication is probably best explained as a result of the polycythemia which is a characteristic finding in patients with the tetralogy of Fallot.

In the field of congenital cardiac disease an interesting syndrome is that of *cerebral abscess developing in the absence* of inflammatory disease in the heart. The syndrome is encountered in about four or five per cent of cases of all major congenital malformations of the heart and great vessels. Classically it is restricted to those hearts in which a venous arterial shunt is possible. The complication is explained as follows. Every person may develop a bacteremia from time to time. This is particularly likely to occur in the presence of an infectious process such as tonsillitis or nasopharyngitis. In normal persons organisms entering the peripheral venous blood pass through the lungs and may be filtered out of the blood stream. If, however, a venous-arterial shunt exists, some venous blood (which may carry bacteria) by-passes the lungs and flows into the systemic circulation without the benefit of the filtering action of the lungs. The peculiar tendency for infection to localize in the brain is not completely understood (Robbins, 1945). Since the tetralogy of Fallot is the most common type of malformation characterized by a venous arterial shunt in which the chances for a relatively long survival are good, it is understandable that this malformation should be the most common one in which the syndrome under discussion is encountered. In about one-half of the patients with the syndrome of cerebral abscess and congenital cardiac disease, the cardiac malformation is the tetralogy of Fallot (Wechsler and Kaplan, 1940, Hanna, 1941, Robbins, 1945; Gates, Rogers and Edwards, 1947; Sancetta and Zimmerman, 1950).

Abbott, Lewis and Beattie (1923) emphasized that the complication of cerebral abscess in congenital cardiac disease may be preceded by an obvious inflammation of another part of the body. One of their patients had acute appendicitis which preceded the development of the cerebral abscess, as proved at necropsy. In another patient of these authors clinical signs consistent with cerebral abscess followed a phlegmon of an arm, but unfortunately the brain was not examined at necropsy.

Cases in which the abscess of the brain was recognized clinically as a complication of congenital cardiac disease are described by Sidenberg and associates (1946), Smolik and associates (1946) and Hand (1947). The patient of Smolik and associates recovered after surgical treatment of the abscess.

There are some who adhere to the concept that *pulmonary tuberculosis* is a common complication in patients who have the tetralogy of Fallot. The diminished pulmonary blood flow is a convenient, if not a critical, explanation for this opinion In his monograph on congenital anomalies of the heart Poynter (1919), discussing cases of pulmonary stenosis, stated, "There seems to be no foundation for the statement, which has been frequently made, that they are particularly subject to pulmonary tuberculosis." In none of the cases of tetralogy of Fallot in the pathologic collection of the Mayo Clinic was active pulmonary tuberculosis associated.

The reader will realize that the foregoing discussion on length of survival and complications in the tetralogy of Fallot pertains to patients who were not treated surgically. With the introduction of surgical treatment for the malformation it is evident that some of the factors discussed

are modified. The condition of the patient who has the tetralogy of Fallot and a functioning anastomosis between a pulmonary and a systemic artery is quite different from that of the untreated patient Comments as to the broad picture of survival and complications in the treated patients will require much time before they can be supported by facts. Certain conjectures are, however, reasonable (Humphreys, 1947).

In the first place, it is apparent, even at this early date, that there will be a material *increase in the length of survival* In large measure this will be influenced by the greater amounts of oxygen in the peripheral arterial blood after operation (Taussig, 1948). The elimination of attacks of intensification of cyanosis and unconsciousness, during which patients may die, is an important favorable factor The increased volume of blood circulating through the lungs as a result of the anastomosis will be expected to lessen the hazard of pneumonia. The patient with high levels of pulmonary blood flow can better withstand the effects of reduced functioning pulmonary parenchyma than the patient with deficient pulmonary blood flow.

It is not anticipated that the basic incidence of subacute bacterial endocarditis will be lowered. Indeed this may conceivably be a more frequent cause of death than in untreated patients. Since patients who are treated are expected to live longer, they will be exposed to the possibilities of this infection over a longer period than patients who die at an early age as a direct result of the pulmonary stenosis Taussig (1948) reported subacute bacterial endocarditis in eight patients following a Blalock-Taussig operation. A new factor that has to be anticipated is the development of bacterial endarteritis in the vicinity of the anastomosis.

In untreated patients congestive cardiac failure is not a major cause of death but it does occur, particularly among the older subjects This factor may become more prominent after operation for two reasons: (1) longer survival causing the right ventricle to be a systemic ventricle for longer periods and (2) the effects of the arteriovenous shunt set into operation by the creation of the anastomosis.

Bahnson and Ziegler (1950) made a *comprehensive study of the causes of* death (99 fatalities) among 500 patients on whom operation was performed at the Johns Hopkins Hospital for congenital cardiac disease of the cyanotic type They found that death was caused by congestive cardiac failure or pulmonary edema in 15 instances. In most instances it was thought that the size of the anastomosis had been larger than ideal. The long-term effect of the shunt is unknown.

Though cerebrovascular complications may be an important cause of death during the operative or early postoperative period (Bahnson and Ziegler, 1950), the patients who pass through this critical period are expected to have less chance of cerebral thrombosis than patients who are not given surgical treatment This favorable prediction is made because successful operation is followed by reduction or disappearance of the polycythemia (Taussig, 1948)

Since the anastomotic operation does not eliminate the shunt of blood from the right ventricle into the aorta, cerebral abscess is expected to continue as a cause of death in the tetralogy of Fallot. Indeed this has been reported as occurring during the early postoperative period (Baker and associates, 1949)

THE EISENMENGER COMPLEX



Figure V-28 Model of the heart in the Eisenmenger complex of a boy 11 months of age. The right ventricle is exposed, showing the biventricular origin of the aorta above a ventricular septal defect. The pulmonary trunk is wide. There is no barrier to pulmonary blood flow (Model prepared by Dr Arthur H Bulbulian.)

Pathologic Aspects

The Eisenmenger complex, an uncommon condition, is characterized by (1) a membranous ventricular septal defect; (2) origin of the aorta either from both ventricles above the defect or entirely from the right ventricle; (3) right ventricular hypertrophy; and (4) absence of pulmonary or subpulmonary stenosis (Abbott, 1925 and 1936). (Plate V-1*b* and Figure V-28.)

Though the aorta arises from both ventricles more commonly than it does exclusively from the right ventricle, the latter phenomenon in itself does not militate against the diagnosis of the Eisenmenger complex. The term "dextroposition of the aorta" is often used to indicate either complete or partial origin of the aorta from the right ventricle. The author prefers not to employ this term, since it is occasionally confused with a right aortic arch. Reports of cases of the Eisenmenger complex in which the aorta arose entirely from the right ventricle include those of Barlow (1876), Schramm (Case 2, 1929) and Saphir and Lev (1941).

The pulmonary trunk always arises entirely from the right ventricle. A characteristic feature is that this vessel is either of normal caliber or, more commonly, wider than normal. Often it is perceptibly wider than the aorta, though the latter is of normal size (Warner, 1945). In the case reported by Talley and Fowler (1936) the disparity between the size of the two great arteries was caused in part by hypoplasia of the ascending aorta.

The pulmonary valve has three cusps. These are usually normal unless involved secondarily by bacterial inflammation. The aortic valve likewise has three cusps but these may be deformed.

In Eisenmenger's (1897) case the right and posterior aortic cusps were deformed and pulled toward the underlying ventricular septal defect. Eisenmenger considered that the aortic valve was competent, however. In the case of Taussig and Semans (1940), on the contrary, similar aortic valvular deformity caused aortic insufficiency. The resulting clinical signs were such as to be confused with the signs of a patent ductus arteriosus. Similarly confusing clinical pictures produced by aortic valvular deformity in association with a membranous ventricular septal defect were reported by Hurst and Schemm (1948) and by Soulié and associates (1949).

The left ventricle is usually of normal size. The frequent but inconstant finding of increased cardiac weight is to a great extent attributable to the right ventricular hypertrophy.

In the case reported by Stewart and Crawford (1933), the heart weighed 600 grams, the patient was a man of 60 Rosedale's (1935) patient was a boy 10 years of age whose heart weighed 310 grams. The same weight was recorded by Millman and Kornblum (1936) in a patient aged 32 years. This figure is within normal limits for a man of this age

Associated cardiovascular malformations may occur In clinical study of a case of the Eisenmenger complex in which the patient was a boy aged 15 years, Glazebrook (1943) demonstrated a right aortic arch roentgenologically In this case the back of the esophagus was compressed, evidently by the aorta From this it may be assumed that the right aortic arch was associated with a left-sided descending aorta In Barlow's (1876) patient, a boy aged three months, there was absence of the aortic arch at the level between the origin of the left subclavian artery and the ductus arteriosus The ductus arteriosus was patent and through it the descending aorta had been supplied with blood A widely patent ductus arteriosus was found by Saphir and Lev in their patient who was 21 years old at the time of death. A persistent left superior vena cava was present in the second case of Schramm (1929)

Historical Aspect of the Eisenmenger Complex

Though the name of Eisenmenger is applied to the condition under discussion, it is agreed that Abbott (1925, 1927) was the one who recognized the peculiar combination of malformations as part of a complex to be separated from uncomplicated defect of the membranous part of the ventricular septum. My associate, Dr. Howard B. Burchell, has expressed the opinion that for this reason the complex should be referred to as the "Eisenmenger-Abbott complex" Though this is a logical attitude it is often difficult to change the designation of a condition even though that designation may be misleading historically. The euphonious name "Eisenmenger complex" would yield with difficulty to a more cumbersome one. Though Eisenmenger (1897) is often given credit for being the first to describe the anatomic characteristics of the condition which bears his name, Dalrymple (1847) described a heart with that condition almost half a century prior to Eisenmenger's contribution. Moreover, the paper of Barlow (1876) also precedes that of Eisenmenger. Eisenmenger's case was described in much more detail than that of Dalrymple or Barlow Eisenmenger's paper is the first to contain illustrations of the condition under discussion.

Functional Disturbances and Pulmonary Vascular Changes

The Eisenmenger complex has a peculiar functional characteristic in that the right ventricle maintains after birth essentially the same function which it has during fetal life in normal persons The right ventricle supplies blood both to the pulmonary circulation and to the systemic circulation (Burchell *et al.*, 1950). Since there is no barrier to pulmonary blood flow in the major arterial pathways it would seem reasonable to suppose that one of the problems for patients with this complex would be excessive pulmonary blood flow. While it is conceivable that excessive flow may cause death in early infancy, such a condition does not seem to be present in those patients who survive.

Bing, Vandam and Gray (1947), who studied five patients with the Eisenmenger complex by cardiac catheterization, fou

that the volume of pulmonary blood flow was within normal limits and that pulmonary hypertension was present.

These observations were explained by the assumption that there was an increased resistance to blood flow through the pulmonary vascular bed. Preliminary pathologic observations indicated that the intrapulmonary arterial tree showed organic changes causing luminal narrowing. Bing and associates suggested that such changes might be the anatomic expression of increased resistance to pulmonary blood flow and to the pulmonary hypertension. Such deductions are supported by the pathologic observations of Stewart and Crawford (1933), Old and Russell (1950) and Civin and Edwards (1950).

Stewart and Crawford reported on a patient, aged 60 years, who had the Eisenmenger complex. In this case the intrapulmonary arteries showed medial hypertrophy and intimal fibrosis. These changes were associated with luminal narrowing. Though the patient had syphilis, these vascular lesions seem not to have resulted from the infection. More recently Old and Russell (1950) reported on the pulmonary vascular changes in a boy, aged 11 years, who had the Eisenmenger complex. Two types of intrapulmonary arterial changes were observed The first was characterized by arterial necrosis. This change conceivably is not related to the cardiac malformation. The second type of lesion, found mostly in the muscular arteries, was characterized by medial hypertrophy, "elastification" of the media and severe intimal fibrosis. These changes were associated with extreme degrees of luminal narrowing. In a younger patient, aged 11 months, studied by Civin and me (1950), the pulmonary muscular arteries showed medial hypertrophy, but no intimal fibrosis. There were noticeable degrees of luminal narrowing. The structural characteristics of the muscular pulmonary arteries in the latter case were abnormal for a child of 11 months but were like those seen normally in the fetus and in infants during the first half-year of postnatal life.

These similarities were considered significant in the following manner. It is assumed that during fetal life, when the right ventricle supplies the lungs as well as the descending aorta, through the ductus arteriosus, some mechanism of a regulatory nature must exist in order that these two regions be supplied with suitable amounts of blood. In the fetus, if resistance to pulmonary blood flow were materially lower than resistance to systemic flow, the lungs would receive great quantities of blood while the lower part of the systemic circulation and the placenta would be deprived. This, however, does not seem to happen in the normal fetus (Hamilton *et al.*, 1937, 1950). It may therefore be assumed that some mechanism exists to cause resistance to pulmonary flow to be of the same magnitude as resistance to systemic flow. Part, at least, of the increased resistance is related to the respiratory dynamics peculiar to the fetus.

Such a mechanism could also employ a state of tone in the intrapulmonary arteries. The finding of thick muscular arteries in the fetal lung is consistent with such an assumption. In the normal person after birth the resistance to pulmonary flow becomes lower than the resistance to systemic flow. This is of no harm to the normal person in whom the ductus arteriosus closes normally after birth. In patients who have the Eisenmenger complex a different situation applies after birth. In these the anatomic peculiarities of the heart are such that the right ventricle continues to supply blood to both circulations. Were there a normal evolution in the the lungs, with the lowering of resistance to pulmonary blood flow the balance of flow from the right ventricle would be upset.

There would be a tendency for blood to flood the lungs and for the systemic circulation to be deprived of it. Such an untoward complication does not seem to occur in those patients who survive (Bing *et al*). Most patients with the Eisenmenger complex after birth seem to continue to have the same type of mechanism controlling flow from the right ventricle that is assumed to exist in the normal fetus. The medial hypertrophy of the muscular arteries of the lungs seen in the Eisenmenger complex (Figure V-29) seems to represent a retention of a fetal type of artery If a regulation such as outlined exists, pulmonary hypertension would be expected as a natural consequence This occurrence was demonstrated by Bing and his associates The intimal fibrous thickening of the pulmonary arteries in the 11-year-old patient of Old and Russell and the 60-year-old patient of Stewart and Crawford seems to be a result of the pulmonary hypertension

It is evident from the above discussion that while the intrapulmonary arteries, by virtue of their medial hypertrophy, may exercise a regulatory mechanism of benefit to the patient in preventing excessive pulmonary blood flow, pulmonary hypertension is necessarily associated When the pulmonary arteries show predominantly muscular changes, it is reasonable to suppose that the caliber of these vessels may change and with it the resistance to pulmonary blood flow Relaxation or contraction of the intrapulmonary arteries may account for the changing volumes of pulmonary blood flow under varying conditions in patients with the Eisenmenger complex, as demonstrated by Bing and associates.

The significance of intimal fibrous thickening is different from that of the medial hypertrophy. While the medial hypertrophy may represent a continuation into postnatal life of a fetal type of pulmonary vessel, the intimal changes are to be interpreted as acquired changes, perhaps secondary to the existence of pulmonary hypertension When intimal fibrous changes develop, the involved artery seems to lose its flexibility At the same time the accompanying accentuation of luminal narrowing raises resistance to pulmonary blood flow This rise may be of such proportion as to exceed the resistance to systemic blood flow When such a condition appears, blood from the right ventricle would tend to flow more readily into the aorta than into the pulmonary trunk Functionally the case of the Eisenmenger complex would acquire a resemblance to that of the tetralogy of Fallot The characteristic late appearance of cyanosis in the Eisenmenger complex may be the clinical manifestation of the development of intimal fibrous changes in the pulmonary arteries

Part of the foregoing discussion is conjecture based on evidence from only a few cases of the Eisenmenger complex in which the intrapulmonary vessels have been studied pathologically More correlative work between functional and pathologic studies is needed to test the validity of the assumptions made.

The above discussion emphasizes that in certain forms of congenital cardiac disease the function of the pulmonary vascular tree is intimately bound to the function of the heart, to avoid consideration of the pulmonary vessels and to study only the heart would result in an incomplete analysis of the situation. The feature in the Eisenmenger complex of a ventricular ejectile force that is common to both circulations, in the absence of a barrier to pulmonary blood flow in the major channels, is also encountered in some other cardiovascular malformations These conditions include cor triloculare biatriatum, persistent truncus arteriosus with wide pulmonary arteries, and coarctation of the



Figure V-29. Sections of lung stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain.

a Intrapulmonary muscular artery in the Eisenmenger complex of an 11-year old child showing medial hypertrophy and some fibrous thickening of the intima The lumen is narrow. The internal and external elastic laminae are prominent and wavy. X 375.

b. A pulmonary artery from a case of the Eisenmenger complex showing medial hypertrophy and considerable intimal thickening leading to marked luminal narrowing.

aorta with patent ductus arteriosus in which the ductus arteriosus enters the aorta distal to the coarctation. (See Coarctation of the Aorta with Patent Ductus Arteriosus)

In addition to the organic changes in the pulmonary vessels as outlined, there may at times be evidence of thrombosis with organization Probably these thrombi result from damage to the vessels incident to the existing pulmonary hypertension

The changes in the intrapulmonary arteries, with the exception of thrombi, in the Eisenmenger complex are in contrast to the appearance of the pulmonary arteries in other congenital malformations in which the right ventricle supplies both circulations but in which there is also pulmonary or subpulmonary stenosis In the tetralogy of Fallot, for example, the right ventricle maintains the same function as in the Eisenmenger complex but in the presence of the characteristic pulmonary or subpulmonary stenosis, medial and intimal changes in the pulmonary arteries are not observed

Of interest is the case of infundibular stenosis with biventricular origin of the aorta reported by Civin and me In this case there were no deviations from normal in the pulmonary arteries It seemed that the infundibular stenosis was of such a degree as would allow adequate pulmonary blood flow and at the same time prevent the development of organic changes in the pulmonary vessels.

Pathologic Distinction Between the Eisenmenger Complex and Ventricular Septal Defect. *The pathologic distinction between the Eisenmenger complex and ventricular septal defect is not always simple.* It may at times be difficult to determine with certainty whether the aorta arises partly from the right ventricle or not *In any case with a* defect of the membranous part of the ventricular septum it is readily possible to pass a probe from the right ventricle into the aorta But this in itself need not constitute proof of the origin of the aorta, in part, from the right ventricle In the first place it must be clearly evident that there is anatomic connection between these two structures If that is lacking, the pathologic diagnosis of the Eisenmenger complex cannot be made At other times the aorta arises partly from the right ventricle but the diagnosis of the Eisenmenger complex cannot be established for yet another reason If the right ventricle fails to show hypertrophy, the diagnosis of the Eisenmenger complex is in doubt The reason for this opinion is that, according to present-day criteria of the Eisenmenger complex, the right ventricle supplies blood both to the aorta and to the pulmonary trunk. In the absence of right ventricular hypertrophy it is doubtful that the right ventricle had assumed such a bilateral function

Additional and helpful evidence may be furnished by studies on the oxygen saturation of the peripheral arterial blood. In the absence of some degree of desaturation of this blood and in the absence of right ventricular hypertrophy, minor de-

Prominence of the elastic membranes X 155 (Material illustrated in *a* and *b* from the case of Old and Russell (1950) which was submitted by the authors and published with their permission)

c Small intrapulmonary muscular artery from a patient at 11 months of age with the Eisenmenger complex The media is thick and the lumen is narrow The picture is like that in the normal newborn (*d*) and in contrast to the picture at a later stage in development (*e*) X 450

d A normal small intrapulmonary muscular artery in an infant four days old The media is thick and the lumen narrow X 450

e A normal small intrapulmonary muscular artery in an infant six months of age The picture is different from that in the newborn period (*d*) and from that in the Eisenmenger complex (*c*) The media has become thin and the lumen wide. X 450.

grees of origin of the aorta from the right ventricle should not be considered to support the diagnosis of the Eisenmenger complex. The problem may be particularly difficult to resolve in young infants on whom oxygen saturation studies of the arterial blood had not been done. This is so because normally the right ventricle is relatively thick in the fetus and during the newborn period At this age, examination of the pathologic specimen alone may not help in resolving the problem as to whether the condition is an uncomplicated ventricular septal defect or an Eisenmenger complex

The distinction between the two conditions may be rendered difficult by yet another set of circumstances. The malformation is primarily an ordinary type of ventricular septal defect which is complicated by occlusive pulmonary vascular changes and associated pulmonary hypertension. If the pulmonary vascular changes are sufficiently severe and widespread, some blood from the right ventricle will enter the aorta Clinically such a case will show many of the features of the Eisenmenger complex: right ventricular hypertrophy, pulmonary hypertension and incomplete saturation of the peripheral arterial blood. In such a case at necropsy the aorta may appear to take origin in part from the right ventricle. Resolution of this problem may possibly be accomplished by a microscopic study of the intrapulmonary vessels. If the malformation had represented the Eisenmenger complex, the changes in the pulmonary arterial vessels would be expected primarily to be medial. Intimal fibrous changes might be superimposed. On the other hand if the malformation had represented a ventricular septal defect which had become complicated by pulmonary hypertension, it would be expected that the predominant changes in the pulmonary vessels would be intimal fibrous thickening.

Complications of the Eisenmenger Complex

Patients who have the Eisenmenger complex may die during early infancy (Barlow, 1876; Clawson, 1944) but many live to adolescence or adult life.

In 1927 Abbott found that in eight cases of this complex the mean age at the time of death was 16 years. This figure may be somewhat low for the over-all picture. Since Abbott's report several other reports have been made concerning older individuals. Notable was the report of Stewart and Crawford describing the complex in a man who was 60 years old at the time of death. Schramm's patients were 48 and 58 years old, respectively; Talley and Fowler's 31 years; Millman and Kornblum's 32 years, and Saphir and Lev's 21 years. Against these older patients are set the five-year-old patient of Warner, the 10-year-old patient of Rosedale and three patients of Clawson all of whom died when less than six months of age.

The cause of death in the early postnatal period is not clear although the possibility of failure of a regulatory mechanism in the pulmonary vessels must be considered. Were the pulmonary arteries to undergo normal postnatal dilatation, the resistance to pulmonary blood flow would fall. As a consequence of this there might be great pulmonary blood flow in association with deficient systemic blood flow. In order to clarify this problem, studies of a functional nature should be made on infants with this complex who fail to compensate for the malformation.

Among the patients who survive the early postnatal periods, two causes of death are paramount: *cardiac failure* and *subacute bacterial endocarditis*. Cerebral abscess is a less common cause. Cardiac failure is predominantly right-sided and

caused to a great extent by the existing pulmonary hypertension. When either pulmonary valvular insufficiency (Talley and Fowler, 1936) or aortic insufficiency (Taussig and Semans, 1940) is present, these additional factors may play a role in causing cardiac failure.

Reported cases in which death was caused by congestive cardiac failure are listed as follows, according to author, and sex and age of the respective patient Dalyrmple, female 25 years, Eisenmenger, male 32 years; Stewart and Crawford, male 60 years; Rosedale, male 10 years, Talley and Fowler, female 31 years, and Saphir and Lev, male 21 years. These cases, except for the one of Dalrymple, are listed in the review of Saphir and Lev (1941)

Bacterial endocarditis follows congestive cardiac failure as the principal cause of death among subjects with the Eisenmenger complex.

In the second case of Schramm and in the case of Millman and Kornblum the infection started on the pulmonary valve In Libman's case, which was reported by Abbott (1925), the endocarditis seemed to have started on the aortic valve and secondarily to have involved the margins of the ventricular septal defect and the aortic leaflet of the mitral valve.

Cerebral abscess without bacterial endocarditis was the cause of death of the patient of Baumgartner and Abbott (1929), a man aged 20 years. The abscess was caused by a hemolytic streptococcus and was situated in the right frontoparietal area

Hoarseness may be a complication of the Eisenmenger complex (Baumgartner and Abbott, Talley and Fowler) It may be troublesome to the patient but is not in itself of serious consequence. Hoarseness is explained as a result of interference with the function of the left recurrent laryngeal nerve by the dilated pulmonary arterial vessels. It will be recalled that hoarseness may be observed in patients with atrial septal defect as the result of a similar phenomenon.

STENOSIS OF OSTIUM INFUNDIBULI

Pathologic Aspects

In 1909 Keith focused attention on a malformation characterized by localized stenosis of the outflow tract of the right ventricle. The level of the stenosis usually lies several centimeters inferior to the pulmonary orifice, thereby converting the right ventricle into two parts (Figure V-30*a*). The caudal portion is composed of the inflow portion and of the inferior part of the outflow tract. The cephalic portion of the right ventricle is the superior portion of the outflow tract, the part of the right ventricle lying superior to the region of stenosis and inferior to the pulmonary valve. The stenosis is usually only of moderate size, often admitting the tip of the index finger (Figure V-30*b*). Of the 19 hearts with this malformation which Keith observed among 270 specimens with various types of congenital cardiac malformations, the diameter of the opening of the stenosis varied from 2 to 15 mm. Characteristically, associated findings are hypertrophy of the right ventricle inferior to the level of stenosis, and little or no hypertrophy of this chamber superior to that level. The endocardium of that part of the right ventricle cephalic to the stenosis often is thickened by fibrous tissue This is probably a reaction to the trauma of blood forcibly ejected throughout the narrow opening. The pulmonary valve is normally constructed and usually is of normal size. Occasionally it may be somewhat dilated.

In nine of the 19 cases which Keith re-

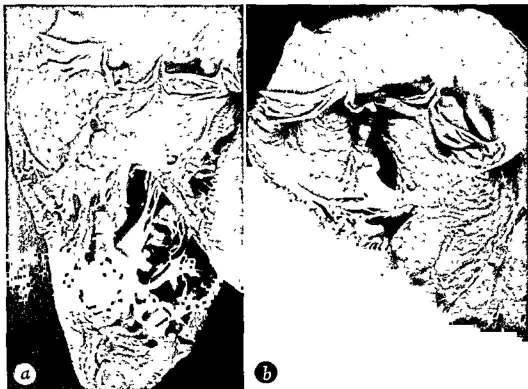


Figure V-30 Stenosis of ostium infundibuli from a 47-year-old man, a patient of Civin and Edwards

infundibuli

viewed, there was an associated defect of the membranous portion of the ventricular septum. In 1933 Eakin and Abbott reported two instances of stenosis of ostium infundibuli in which the ventricular septum was closed. They stated that a ventricular septal defect is almost always associated with stenosis of ostium infundibuli and therefore considered their two cases as being unusual. They cited only two other examples of stenosis of ostium infundibuli in which a closed ventricular septum was present. These were the cases of Laffitte (1892) and Clarke (1893). It is evident that their opinion as to the rarity of closed ventricular septum in association with the malformation being considered is somewhat at variance with the earlier findings of Keith. They did not include in their review Leitmann's (1928) case in which the ventricular septum was closed Cases of stenosis of ostium infundibuli with closed ventricular septum reported since the time of Eakin and Abbott's paper include those of Carr and Levi (1939), and Konwaler (1944).

When the ventricular septum is defective, biventricular origin of the aorta may be associated, as in the cases of Dryerre and Walmsley (1939), Abbott (Case 3, 1925), and Civin and Edwards (1950) When the ventricular septum is closed, the aorta, though communicating only with the left ventricle, may be displaced to the right and there may be an aneurysm of the membranous septum (Eakin and Abbott, Carr and Levi).

The case of Dryerre and Walmsley was unusual in that in addition to a ventricular septal defect there was also a communi-

cation between an aortic sinus and the right ventricle inferior to the level of stenosis. In Konwaler's case the stenosis of ostium infundibuli was represented by three openings rather than one

Functional Disturbances

The functional disturbances of stenosis of ostium infundibuli depend on whether or not a ventricular septal defect is associated.

If the ventricular septum is closed the functional disturbances caused by the stenosis are similar to those in isolated pulmonary stenosis. There is no opportunity for venous blood to be shunted from the right ventricle into the aorta If, on the other hand, a ventricular septal defect is associated, the caudal part of the right ventricle communicates with the left ventricle or, if biventricular origin of the aorta is also present, with the aorta. Under the latter circumstances particularly, the right ventricle may supply blood to the aorta. In this instance the peripheral blood may fail to be completely saturated with oxygen. In contrast to the tetralogy of Fallot, pulmonary blood flow may approach normal volumes.

In spite of the presence of hypertension in the lower part of the right ventricle, pulmonary hypertension does not seem to exist.

In the case which Civin and I studied (1950), the aorta had a biventricular origin superior to a ventricular septal defect. Yet the intrapulmonary arteries and arterioles were normal. These findings were in contrast to those in the Eisenmenger complex. We postulated that the zone of stenosis in the outflow tract of the right ventricle had been responsible for the absence of organic changes of the arteries within the lung (Figure V-31). Support of the interpretation, made on morphologic grounds, that pulmonary hypertension does not ordinarily exist in

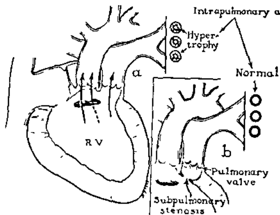


Figure V-31 A diagrammatic comparison of the cardiopulmonary vascular dynamics in the Eisenmenger complex (*a*) and in stenosis of ostium infundibuli associated with biventricular origin of the aorta (*b*) In the Eisenmenger complex there is pulmonary hypertension incident to increased resistance to flow at the level of the intrapulmonary muscular arteries This is related to organic occlusive changes in the intrapulmonary arteries In contrast, in infundibular stenosis with biventricular origin of the aorta the stenosis of the outflow tract of the right ventricle seems to be the basis for absence of pulmonary hypertension and of organic changes in the pulmonary arteries.

stenosis of ostium infundibuli is given by catheterization studies (Dow *et al.*, Case 2, 1950, Case of Willius, Dry and Wood in Civin and Edwards, 1950).

Complications

The chances for survival for a number of years of patients who have stenosis of ostium infundibuli are relatively good In the majority of cases reported the patients had lived beyond adolescence, into early adult life.

The case of Carr and Levi (1939) is somewhat exceptional in that the patient lived to the age of 65 years, dying of congestive cardiac failure at that time. Acquired calcific aortic stenosis was also present in this case so that the failure of the heart might have been caused by two factors rather than the stenosis of ostium infundibuli alone. The patients of Leitmann and of Civin and Edwards each died at 47 years of age.

The most common cause of death of

patients who have stenosis of ostium infundibuli is subacute bacterial endocarditis. The endocarditis appears to start on the margins of the stenotic area, presumably at the site where the blood produces the greatest trauma by passing through the narrowed zone The vegetations may be very large and often extend to involve the wall of the right ventricle above the level of the stenosis, and to the pulmonary valve

The following authors have reported instances of this malformation complicated by subacute bacterial endocarditis (the age of the patient at death being indicated): Laffitte (1892), 21 years; Clarke (1893), 21 years, Abbott (1925), Case 3, 22 years; Leitmann (1928), 47 years; Eakin and Abbott (1933), Case 2, adult woman, Dryerre and Walmsley (1939), 17 years, Lev and Strauss (1942), 35 years, Konwaler (1944), 23 years. Congestive cardiac failure as a cause of death is less common than bacterial endocarditis.

SUBAORTIC STENOSIS

Pathologic Aspects

In subaortic stenosis the outflow tract of the left ventricle shows localized narrowing Keith (1909) compared the stenosis of the left ventricular outflow tract in this condition to stenosis of ostium infundibuli of the right ventricle.

The most striking change in the fully established case is that the endocardium of the outflow tract of the left ventricle is thickened, gray and opaque. The lower margin of the thickened endocardium projects as a ridge or shelf facing caudally into the lumen of the left ventricle. This ridge, composed of elastic and collagenous tissue, not only involves that portion of the outflow tract of the left ventricle formed by the ventricular septum but is also present on the neighboring ventricular surface of the anterior leaflet of the mitral valve. This appears to produce a stenosing fibrous collar in the left ventricular outflow tract (Figure V-32*a*). In some descriptions of subaortic stenosis this feature is the sole one mentioned. Some defects show a peculiar bulge on the part of the ventricular septum, as in the case of Greenberg and Simon (1949), *i.e.*, the ventricular septum extends farther to the left than normal and so extends into the path of the outflowing left ventricular blood. At other times, though the ventricular septum is intact, the base of the aorta lies more to the right than normal. In Rae's case (1936), there was also an aneurysm of the membranous portion of the ventricular septum.

The channel of the left ventricular outflow tract at the level of stenosis is usually so reduced in diameter as to admit only the examiner's little finger. This is in contrast to the common occurrence of a normal caliber of the aortic valve (Figure V-32*b*) Typical features of this condition were clearly illustrated in 1875 by Lauenstein. Though the aortic valve is usually normal and its orifice of normal size, in a few reported cases there have been aortic valvular malformations.

Dilg in 1883 reported subaortic stenosis in a patient two years of age and reviewed 15 cases reported earlier; he stated that in his case and in Bouillard's there were bicuspid aortic valves.

The case of Walsh and associates (1943) exhibited a large posterior and two smaller anterior aortic leaflets. According to these authors a bicuspid aortic valve was present in the patient of Thursfield and Scott. In Dormanns' patient (1939), a laborer aged 16 years, the aortic valvular cusps were underdeveloped and composed of myxoma-like tissue.





Figure V-32 Subaortic stenosis in a man aged 26 years
a The unopened fibrous collar in the outflow tract of the left ventricle
b The unopened aortic orifice is viewed from above The aortic valve is normal and beneath it is the subaortic stenosis

In Case 1 of Morrison and Edwards (1950) the patient was a man aged 26 years who died of congestive cardiac failure and presented a patent ductus arteriosus associated with his defect

Functional Disturbances

The chief functional disturbance of subaortic stenosis is strain of the left ventricle with resulting hypertrophy of its wall This often causes increased cardiac weight (Greenberg and Simon, 1949).

Complications

Cardiac failure may thus play a role in death of the patient. Many of the patients live to adult life (Gruenwald, 1947) and in some the lesion is incidental to other unrelated diseases. There is great danger, however, that in a case of subaortic stenosis *bacterial endocarditis* will develop This inflammatory process may originate on the rim of fibrous tissue (Gruenwald, 1947), presumably at the zone of greatest mechanical stress, or it may originate on the aortic valve (Wiglesworth, 1937, Mason and Hunter, 1942).

In the patient of Walsh and associates the bacterial endocarditis probably originated on the deformed aortic valve and involved the subaortic shelf and the mitral valve secondarily In the second case of Morrison and Edwards (1950) bacterial endocarditis involved the aortic valve and the subaortic shelf of fibrous tissue (Figure V-33) Though a decision could not be reached as to the site of origin of the infection, the inflammation was probably primary on the aortic valve. Dormanns' (1939) patient, a boy of 16, died suddenly

In 1937 Wiglesworth stated that he was able to find only 36 cases of subaortic stenosis in the literature.

Gruenwald reported on six cases which were found at necropsy at the Mount Sinai Hospital in New York City over a period of only seven years Gruenwald expressed the opinion that the condition is probably more common than is evident from the number of cases reported. Walsh and asso-



Figure V-33 Subacute bacterial endocarditis ... ing the aortic valve and the subaortic shelf ... aortic stenosis From a man aged 25 years

ciates stated that no example of subaortic stenosis was found among more than 10,000 necropsies at the Massachusetts General Hospital in Boston. Six well-established examples of this condition are among the 212 examples of major cardiac and vascular malformations in the Mayo Clinic pathologic collection.

TAUSSIG-BING COMPLEX

Taussig and Bing (1949) described a complex consisting of a transposed aorta, a large pulmonary trunk which arises primarily from the left ventricle and partially overrides the ventricular septum, a "high" ventricular septal defect, and right ventricular hypertrophy. They named the malformation "complete transposition of the aorta and a levoposition of the pulmonary artery." Since this malformation is in essence a complex not fully defined by the name given to it by the original authors and since some of the developmentally related malformations bear such eponymic names as the "tetralogy of Fallot" and the "Eisenmenger complex," it seems appropriate to call this condition the "Taussig-Bing complex."

In the Taussig-Bing complex (Figure V-34) the aorta lies in a plane ventral to, and to the right of, the pulmonary trunk. It arises entirely from the right ventricle. The aortic origin is separated from the pulmonary origin and from the ventricular septal defect by a ridge of muscle, probably the crista supraventricularis. Since the venous connections of the heart are normal, the aorta is supplied by a mixture of blood composed in part of blood entering the right side of the heart through the great veins and in part of oxygenated blood entering the right ventricle through the ventricular septal defect. The pulmonary trunk arises approximately in a normal position as judged from the external appearance of the heart. From within the heart it is seen that the pulmonary trunk arises primarily from the left ventricle but in overriding the defect of the membranous part of the ventricular septum, it arises in part from the right ventricle as well The pulmonary trunk is wider than normal and wider than the aorta.

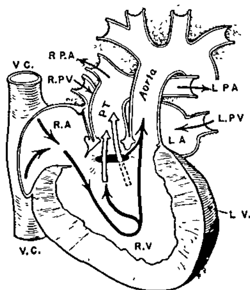


Figure V-34. The intracardiac circulation in the Taussig-Bing complex. (Modified from Taussig and Bing, 1949.)

In the heart described by Taussig and Bing there was only a moderate difference between the caliber of the two vessels In a case which Dr. Taussig had been shown on the occasion of a visit to Norway the aorta was narrower than the pulmonary trunk. Taussig and Bing listed the points of similarity between the Eisenmenger complex and the syndrome which they described. These are: origin of the pulmonary trunk at least in part from the right ventricle; large pulmonary arteries which on roentgenoscopy usually show expansile pulsations, and prominence of the pulmonary conus on roentgenologic examination; a systolic murmur; right ven-

tricular hypertrophy and pulmonary hypertension; survival of the patient for a number of years.

Certain differences exist between the Eisenmenger complex and the Taussig-Bing complex. The outstanding clinical difference is that in the Taussig-Bing complex, cyanosis dates from birth while in the Eisenmenger complex it is characteristic for cyanosis to develop at about the time of puberty. Clubbing of the fingers and toes and polycythemia, while developing in each of the two conditions, tend to occur later in the Eisenmenger complex than in the Taussig-Bing complex

The chief anatomic difference between the Eisenmenger complex and the Taussig-Bing complex is that in the former the aorta arises in part from each ventricle, while in the latter it arises entirely from the right ventricle. Moreover, in the Eisenmenger complex the pulmonary trunk arises entirely from the right ventricle while in the Taussig-Bing complex the pulmonary trunk arises from each ventricle. In the Taussig-Bing complex a catheter placed in the right side of the heart may be passed either into the aorta or into the pulmonary trunk The oxygen saturation of the blood in the pulmonary trunk is greater than that in the aorta or the peripheral arteries Observations such as these are critical in establishing the presence of the Taussig-Bing complex when other clinical data are equivocal In the Eisenmenger complex the blood in the aorta or in its branches is characterized by a greater degree of oxygen saturation than the blood in the pulmonary arterial system

In the report of Taussig and Bing it was stated that many of the pulmonary arterioles showed diffuse intimal proliferation which rendered the lumina of these vessels extremely narrow. No mention was made of any medial changes in these vessels and in the smaller pulmonary arteries. The narrow state of the arteriolar lumina served as an explanation of increased resistance to pulmonary blood flow. This resistance probably was responsible for the moderate degree of pulmonary hypertension as determined by cardiac catheterization As in certain other conditions in which the propelling force is common to the two circulations, and in spite of the wide pulmonary trunk, it is likely that the occlusive vascular changes in the smaller pulmonary vessels were responsible for a reasonable balance of flow to the two circuits and for sufficient cardiovascular efficiency to maintain life for some years. The patient of Taussig and Bing died at the age of 5½ years while angiocardiography was being performed Lev and Volk (1950) described an instance of this malformation in a one-year-old male infant.

COMPLETE TRANSPOSITION OF THE GREAT VESSELS

Pathologic and Functional Features

Transposition may be defined as any congenital abnormality in the relationship of the great arterial vessels to each other and to the cardiac ventricles. The tetralogy of Fallot, the Eisenmenger complex, the Taussig-Bing complex, and persistent truncus arteriosus may be considered as varieties of transposition. In this section, however, we are concerned with yet another and well-defined condition designated as *complete transposition of the great vessels.* This condition is one in which the aorta arises exclusively from the right ventricle and the pulmonary trunk exclusively from the left ventricle (Figures V-35 and V-36*a*). The aorta lies ventral to and on a plane slightly to the right of the pulmonary trunk. The two

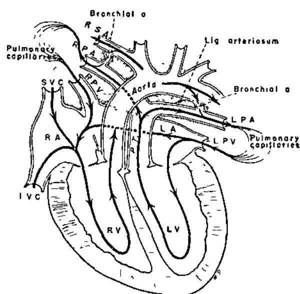


Figure V-35 Complete transposition of the great vessels Diagrammatic representation of Cockle's case (1863) in which the two sides of the circulation communicated by means of dilated bronchial arteries and a patent foramen ovale.

vessels run parallel to each other This anatomic arrangement is responsible for the narrow shadow cast by these two vessels in the anteroposterior view of the roentgenogram The latter phenomenon has been emphasized by Taussig (1938) as an important diagnostic characteristic for complete transposition of the great vessels These two vessels fail to cross each other as they normally should. In some cases in which the great vessels are interrelated, as in complete transposition, there is a single ventricle anatomically In still other instances there are two ventricular chambers but there is atresia of either the mitral or the tricuspid valve In such a case the ventricular chambers function together as though one chamber existed It seems advisable to reserve for the class of malformations termed *complete transposition of the great vessels* those cases in which there are two ventricles, anatomically and functionally. To do otherwise brings in under the same name a variety of conditions which function quite differently. Such a broad grouping leads to confusion and causes one's attention to be diverted from the simple fact that complete transposition of the great vessels is an entity with rather clear-cut clinical and pathologic features.

It is essential to distinguish those cases of transposition in which the two ventricles function as separate ventricles from cases with transposition in which the ventricular part of the heart is either single or, if separated into two chambers, functions as a single ventricle. In the former condition (complete transposition of the great vessels) the basic and important consideration is that the blood which has passed through the lungs is unable to reach the aorta and be carried to the greater circulation. In the second group, the abnormal position of the vessels is in itself of little functional consequence since the venous and oxygenated blood which flows through the ventricular part of the heart is mixed blood. In the second group, the *volume* of flow into the aorta may be different from that into the pulmonary trunk because of inherent differences in the caliber of the arterial trunks or of the outlets of the ventricular part of the heart inferior to them; the *character* of the blood, however, which flows into these two tracts is the same, and the systemic circulation receives relatively large amounts of blood that is oxygenated or relatively rich in oxygen, as compared with conditions in complete transposition of the great vessels Ususally in complete transposition (Figure V-35) the right atrium communicates in a normal manner with the venae cavae and the coronary sinus, and also with the right ventricle through the tricuspid orifice. The left atrium receives the pulmonary veins and empties its blood through the mitral valve into the left ventricle. The severe cyanosis characteristic of this condition results from origin of the aorta from the right ventricle (carrying venous blood) while the pulmonary trunk arises from the left ventricle (carrying oxygenated blood). In the

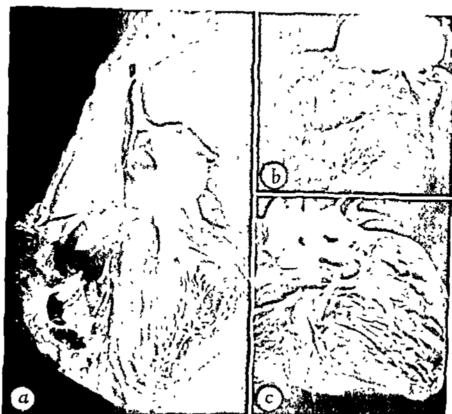


Figure V-36 Complete transposition of the great vessels

a. The aorta arises from the right ventricle and the pulmonary trunk from the left ventricle The ductus arteriosus is patent From a male infant three months old (Reproduced by permission of *Postgraduate Medicine*)

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arteries, which arise from the aorta From a female infant seven months old.

basic malformation there is no arrangement for orderly passage of venous blood through the lungs and then to the systemic arterial circulation. If life is maintained after the umbilical cord is interrupted it means that some sort of communication, however small, must exist between the lesser and greater circulations or between the two sides of the heart.

The three most common means of communication are patent foramen ovale, ventricular septal defect and patent ductus arteriosus (Figure V-36) In a given case one, two or all three of these may be present. Hanlon and Blalock (1948) have reviewed the literature on the subject of complete transposition of the great vessels and have studied the cases of this condition in which necropsy had been performed at the Johns Hopkins Hospital As a result of their studies they have reiterated the postulate that in complete transposition of the great vessels, the more of these three types of communication, the better the chance for survival They have also emphasized that the larger these communications, the better the outlook Of the three types of communication named, they found atrial septal defect in the form of probe-patency of the foramen ovale to be the most common. Ventricular septal defect was less common, occurring in about one-third of the cases.

In four of five cases of complete trans-

position of the great vessels with necropsy which Lichtenstein and Mannheimer (1949) studied there was a ventricular septal defect. A ventricular septal defect is present in only 7 of the 15 specimens with this malformation in the Mayo Clinic pathologic collection. One of these specimens was contributed by Dr. Donald L. Alcott Gibson and Clifton (1938) found a ventricular septal defect in five of nine cases

The defect of the ventricular septum characteristically lies in the region of the membranous portion (Figure V-36*c*), and is usually less than 1 cm. in diameter in hearts of newborn infants. It has been emphasized that those instances in which the defect of the ventricular septum is so large as, in effect, to create a single ventricle should not be classified as examples of complete transposition of the great vessels. Lev and Saphir (1937) have indicated that when the ventricular septum is closed it is formed entirely of muscular tissue.

The direction of flow through a patent ductus arteriosus or across a defect in either of the cardiac septa is not definitely known. Indeed it may vary from case to case and, perhaps, in a given case from time to time Hanlon and Blalock (1948) and Campbell and associates (1949) have suggested that when the volume of blood on one side of the heart becomes significantly greater than on the other side, the pressure rises on the side to which the blood is shunted, causing reversal of the shunt.

In discussing the direction of flow through a ventricular septal defect in one of their cases of complete transposition of the great vessels, Becker and Brill (1948) suggested that during ventricular systole the flow was from left to right, but during diastole the flow might have been from the right ventricle into the left. In King's case (1844) there were a true patency of the foramen ovale and a ventricular septal defect. King postulated that oxygenated blood from the left atrium flowed into the right atrium through the atrial septal defect and that mixed blood passed from the right ventricle into the left through the ventricular septal defect.

Of interest from the point of view of the direction of blood currents is the case of Dreyfuss (1929) whose patient with complete transposition of the great vessels was six days old at the time of death. A patent ductus arteriosus was present, the aortic mouth of which was distal to a coarctation of the aorta. In addition, a patent foramen ovale and a ventricular septal defect were also present. The right ventricular chamber was small, the left being about four times as large. It is evident that the oxygenated blood leaving the left ventricle reached the lower part of the body through connection of the patent ductus arteriosus with the aorta distal to the aortic coarctation. This situation might be called "partial correction of transposition," since in spite of the transposition, the cardiovascular connections partially tended to overcome the potential effects of the basic malformation. In Dreyfuss' case, in spite of correction of the transposition with regard to circulation to the lower part of the body, the upper part was subjected to deficiency of oxygen characteristic of other cases of complete transposition of the great vessels. In cases of transposition with a patent ductus arteriosus but without coarctation of the aorta, the direction of flow through the ductus arteriosus is probably from pulmonary artery to aorta, though this is conjectural. Indeed, it is possible that from time to time the direction of the flow of blood through the ductus arteriosus changes as one of the two circulations becomes overloaded with blood while the other, because of a certain direction of flow, becomes depleted.

Additional sources of communication

between the two circulations may exist and should be sought by the pathologist in all cases of this condition in which necropsy is done. Anomalous drainage of one or several pulmonary veins into the right atrium or one of its tributaries would be a means of getting a substantial amount of arterialized blood into the right side of the heart and so to the aorta for distribution to the systemic circulation.

This was the case in the patient of Feldman and Chalmers (1933), who lived to the age of two months; all of the pulmonary veins entered the right atrium A patent foramen ovale was the avenue by which the left side of the heart received blood.

Abbott (1937) stressed that dilated bronchial arteries may be another important channel of getting the blood from one system into the other in complete transposition of the great vessels.

Cockle (1863) reported a case in point. His patient was a boy who died at the age of two years and eight months. In addition to complete transposition of the great vessels the necropsy revealed an atrial septal defect in the form of a patent foramen ovale, and the mediastinal vessels leading to the lungs were greatly dilated. These were probably bronchial arteries. The ventricular septum and the ductus arteriosus were closed (Figure V-35) This case is important since it demonstrates that in nature there may be important compensatory changes that may be simulated surgically, as in the technics described by Hanlon and Blalock (1948) and Blalock and Hanlon (1950). The dilated bronchial arteries may be compared to the anastomotic channel created by the Blalock-Taussig operation or by the operation of Potts, Smith and Gibson Through these channels venous blood in the aorta is carried to the lungs for oxygenation. The patent foramen ovale may be compared to a surgically-created atrial septal defect through which oxygenated blood can flow from the left atrium into the right for ultimate delivery to the aorta.

The cases of Alexander and White (1947) and of Lawson (1947) seem similar to those of Cockle In each there was an atrial septal defect and evidently a closed ductus arteriosus and no ventricular septal defect Unfortunately in neither case was the state of the bronchial arteries described. The patient of Alexander and White was 17 years old at the time of death and that of Lawson, six years.

In a male infant, aged 22 months, with complete transposition of the great vessels, Harris, Gray and Whitney (1927) reported that an anomalous vein connected the right internal jugular vein with the left atrium. In addition, there was an atrial septal defect represented by incomplete guarding of the foramen ovale by its valve, a ventricular septal defect and a patent ductus arteriosus. It is conceivable that the anomalous vein played a role either in bringing venous blood to the left side of the heart for oxygenation in the lungs or in carrying oxygenated blood from the left atrium to the right side of the heart and so to the aorta The fifth case of Read and Krumbhaar (1932) presented a similar venous variation, the azygos vein communicating with the left atrium.

Becker and Brill (1948) reported that pulmonary stenosis is commonly associated with complete transposition of the great vessels, being mentioned in more than one-third of the reported instances of the malformation. The case of Lewis (1948) is an example of such an association. Bicuspid pulmonary valve may at times be present as in the fourth case of Hemsath and associates (1936). The right atrium is often dilated. Usually the auricular appendages lie in a normal position. In the case of Miskall and Fraser (1948) the right auricular appendage lay to the left of the great arterial vessels and just to the

that up to 1923 there had been 16 reported examples of this malformation and that a ventricular septal defect was present in every instance.

Walmsley's patient did not have a septal defect and so was considered by the author to be unique and perfectly "corrected." The malformation in the case of Roos, which is illustrated in Abbott's Atlas (1936), evidently did not have an associated ventricular septal defect.

Brown's (1939) patient, a girl aged 10 months, had a ventricular septal defect. Grunmach's (1890) patient, a cyanotic boy aged 15 years, had a ventricular septal defect, a patent foramen ovale and stenosis of the pulmonary valve, and also exhibited isolated dextrocardia.

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PERSISTENT TRUNCUS ARTERIOSUS

Classification and Associated Pathologic Features

Persistent truncus arteriosus is characterized by the presence of but one arterial vessel leaving the ventricular part of the heart. There must not be a remnant, in fact or implied, of a second vessel. From the ascending portion of the single vessel the coronary arteries and usually the pulmonary arteries arise. The vessel then continues as the aorta. In an exceptional instance there are no pulmonary arteries. In such a case the condition may be considered as a form of persistent truncus arteriosus if the lungs are supplied by branches of the descending aorta and not by a patent ductus arteriosus.

In 1949, Collett and the author reported a review of the literature on the subject of persistent truncus arteriosus. The chief sources of information used were the classic reviews of Taruffi (1875), Vierordt (1898), Herxheimer (1910), Abbott (1931), Humphreys (1932) and Lev and Saphir (1942). Numerous other reports of cases not covered by these reviews were included in our analysis of a total of 116 cases. Eighty of these cases were considered to be examples of *persistent truncus arteriosus* and 13 of *partial persistent truncus arteriosus.* Of the other 23 cases, 12 were not true examples of this entity even though they had formerly been considered as such by other authors. The remaining 11 cases seemed to be examples of persistent truncus arteriosus but could not be classified because of inadequate information as to the pulmonary arterial supply

The 80 cases of persistent truncus arteriosus were divided into four types, depending on the manner in which the lungs were supplied with arterial vessels (Table

TABLE V-2
Manner in Which Truncus Arose from Ventricular Part of Heart in 80 Cases of Persistent Truncus Arteriosus Classified by Collett and Edwards (1949) According to the Four Types of the Malformation in Their Classification (*Reproduced by Permission of the W. B Saunders Co.*)

Origin of Truncus	*Number of Cases*				
	Type 1	*Type 2*	*Type 3*	*Type 4*	*Total*
From both ventricles (overriding septal defect)	17	11	3	7	38
From right ventricle	7	3	4	2	16
From left ventricle	2	0	0	0	2
From single ventricle	8	9	2	0	19
Unknown	*4*	*0*	*0*	*1*	*5*

V-2) The four types were subdivided according to the direction of the aortic arch and the presence or absence of the ductus arteriosus. The characteristics of the four major types follow:

Type 1 A single pulmonary trunk and the ascending aorta arise from the truncus arteriosus (Figure V-37*a*).

Type 2 The right and left pulmonary arteries arise close together from the dorsal wall of the truncus arteriosus (Figure V-37*b*).

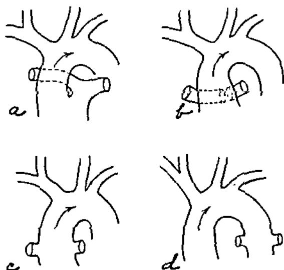


Figure V-37. The four types of persistent truncus arteriosus *a* Type 1. *b* Type 2 *c*. Type 3. *d* Type 4 (From Collett and Edwards Reproduced by permission of the W. B. Saunders Co.)

Type 3. One or both pulmonary arteries arise independently from either side of the truncus arteriosus (Figure V-37*c*).

Type 4 The pulmonary arteries and the ductus arteriosus are absent. The sixth aortic arches are apparently absent. The arterial circulation to the lungs is furnished by the bronchial arteries (Figure V-37*d*).

Type 1. Type 1 was represented by 38 cases which are subdivided according to seven different anatomic variations In each case a short pulmonary trunk and ascending aorta arose from the truncus arteriosus (Figure V-38). The first subdivision comprised 21 cases in which the aortic arch turned to the left, the ductus



Figure V-38. Persistent truncus arteriosus, Type 1. The right ventricle has been opened showing the origin of the persistent truncus arteriosus from both ventricles above a septal defect A short pulmonary trunk gives rise to the right and left pulmonary arteries (From Dry and associates Reproduced by permission of *Postgraduate Medicine.*)

that up to 1923 there had been 16 reported examples of this malformation and that a ventricular septal defect was present in every instance.

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The 80 cases of persistent truncus arteriosus were divided into four types, depending on the manner in which the lungs were supplied with arterial vessels (Table

between the two circulations may exist and should be sought by the pathologist in all cases of this condition in which necropsy is done. Anomalous drainage of one or several pulmonary veins into the right atrium or one of its tributaries would be a means of getting a substantial amount of arterialized blood into the right side of the heart and so to the aorta for distribution to the systemic circulation

This was the case in the patient of Feldman and Chalmers (1933), who lived to the age of two months, all of the pulmonary veins entered the right atrium A patent foramen ovale was the avenue by which the left side of the heart received blood.

Abbott (1937) stressed that dilated bronchial arteries may be another important channel of getting the blood from one system into the other in complete transposition of the great vessels

Cockle (1863) reported a case in point His patient was a boy who died at the age of two years and eight months. In addition to complete transposition of the great vessels the necropsy revealed an atrial septal defect in the form of a patent foramen ovale, and the mediastinal vessels leading to the lungs were greatly dilated. These were probably bronchial arteries The ventricular septum and the ductus arteriosus were closed (Figure V-35). This case is important since it demonstrates that in nature there may be important compensatory changes that may be simulated surgically, as in the technics described by Hanlon and Blalock (1948) and Blalock and Hanlon (1950) The dilated bronchial arteries may be compared to the anastomotic channel created by the Blalock-Taussig operation or by the operation of Potts, Smith and Gibson Through these channels venous blood in the aorta is carried to the lungs for oxygenation. The patent foramen ovale may be compared to a surgically-created atrial septal defect through which oxygenated blood can flow from the left atrium into the right for ultimate delivery to the aorta

The cases of Alexander and White (1947) and of Lawson (1947) seem similar to those of Cockle. In each there was an atrial septal defect and evidently a closed ductus arteriosus and no ventricular septal defect. Unfortunately in neither case was the state of the bronchial arteries described. The patient of Alexander and White was 17 years old at the time of death and that of Lawson, six years.

In a male infant, aged 22 months, with complete transposition of the great vessels, Harris, Gray and Whitney (1927) reported that an anomalous vein connected the right internal jugular vein with the left atrium. In addition, there was an atrial septal defect represented by incomplete guarding of the foramen ovale by its valve, a ventricular septal defect and a patent ductus arteriosus It is conceivable that the anomalous vein played a role either in bringing venous blood to the left side of the heart for oxygenation in the lungs or in carrying oxygenated blood from the left atrium to the right side of the heart and so to the aorta. The fifth case of Read and Krumbhaar (1932) presented a similar venous variation, the azygos vein communicating with the left atrium.

Becker and Brill (1948) reported that pulmonary stenosis is commonly associated with complete transposition of the great vessels, being mentioned in more than one-third of the reported instances of the malformation. The case of Lewis (1918) is an example of such an association. Bicuspid pulmonary valve may at times be present as in the fourth case of Hemsath and associates (1936). The right atrium is often dilated. Usually the auricular appendages lie in a normal position. In the case of Miskall and Fraser (1948) the right auricular appendage lay to the left of the great arterial vessels and just to the

right of the left auricular appendage. Such an anatomic arrangement is in itself of no functional consequence. In the usual instance the two ventricular walls are about equal in thickness, each being hypertrophied. The coronary arteries arise from the aorta.

Incidence and Survival

Complete transposition of the great vessels is relatively common among collections of congenital cardiac malformations taken from infants and children.

Gibson and Clifton (1938) observed this nine times in 105 specimens of congenital cardiac disease from infants and children Terplan and Sanes (1936) found 21 cases of congenital cardiac disease, including one instance of complete transposition among 336 infants up to one year of age on whom necropsy had been performed. Nicholson (1936) found two cases of complete transposition of the great vessels among 37 cases of congenital cardiac malformations In the Mayo Clinic pathologic collection there are 15 examples of this malformation among 212 specimens of major malformations of the heart and great vessels. Mannheimer (1949) observed six examples of complete transposition of the great vessels among 114 cases of congenital cardiac disease with cyanosis.

There is a predilection for the male sex, the ratio being about three males to one female. Of the 15 instances in the Mayo Clinic collection, in ten the subjects were males and in five females.

Kato (1930) made an extensive review of reported instances of complete transposition of the great vessels and emphasized that most patients who have this condition do not survive beyond infancy, although he cited instances in which patients reached adolescence or adult life. Hanlon and Blalock (1948) reviewed the survival time in 123 cases of transposition taken from the following sources: 85 of the 97 cases reviewed by Kato in which data were sufficient for analysis; isolated case reports after the time of the publication of Kato's paper, and 23 cases studied at necropsy at the Johns Hopkins Hospital. The average duration of life in this series of 123 cases was 19 months. They stated that if the six patients who survived 10 years or longer were removed from the series the average age at death of the remaining 117 patients would be 5½ months. These authors emphasized the importance of communications between the two sides of the heart, namely, atrial septal defect, ventricular septal defect, and also patent ductus arteriosus. They emphasized particularly the beneficial effects of a ventricular septal defect and of combinations of intercommunication.

These points were supported by the cases of Wenner (1909), Jacobson (1921), Moore (1929), Lia and Leary (1939), Walker and Dardinski (1945), and many others. In one of the 15 cases in the Mayo Clinic collection the patient lived seven and a half years. The remaining ones died during infancy. The ages at death in the nine cases of Gibson and Clifton were as follows. one month or less, five cases; first year of life, three cases; and two years and one month, one case.

Four examples of complete transposition of the great vessels are described in the comprehensive report of Harris and Farber (1939) on transposition of the great vessels. The youngest patient was a girl who died at the age of four weeks. The ductus arteriosus was patent but the atrial and ventricular septa were closed. In a 35-day-old boy the foramen ovale was patent, the ventricular septum had a tiny opening and the ductus arteriosus was closed. A male patient aged 4½ months had no patency of the atrial septum but a ventricular septal defect and a patent ductus arteriosus. Their oldest patient was a

boy aged eight months in whom the ductus arteriosus was closed but the ventricular septum and the foramen ovale were patent

Several of the cases reviewed by Kato which favorably influence the average age of survival should not be included under the designation of complete transposition of the great vessels For example, there is included the case of Hedinger (1915), that of a woman aged 56 years with transposition of the great vessels but also with tricuspid atresia (see Section IV) In this patient the ventricular part of the heart functioned as a single chamber The defect should better be classified as tricuspid atresia with transposition of the great vessels and subpulmonary stenosis rather than as an example of complete transposition of the great vessels In Buchanan's (1857) case the patient was a boy aged four years in whom the pulmonary trunk arose from the left ventricle but the aorta arose from both ventricles above a ventricular septal defect The patient of Lewis and Abbott (1915), a man 21 years old, clearly had a cor triloculare biatriatum with transposition Ball's (1926) patient aged two and one-half years had a similar condition, as did the patient of Carns, Ritchie and Musser (1941), a woman aged 44 years. The defect in the latter patient was designated by Lawson as an example of complete transposition of the great vessels

The patient of Schilling (1857) was a male infant aged 15 months in whom the aorta arose from the left ventricle and the pulmonary trunk from both ventricles above a ventricular septal defect A case of Keith (1912), in which the patient was 16 years old, presents difficulty in classification In this patient the aorta arose from the right ventricle and the pulmonary trunk from the left, the foramen ovale was open, and a ventricular septal defect was described as large This defect in effect might be considered to represent a single ventricle. It demonstrates, as others have stressed, the beneficial effect of free mixing of blood between the two sides of the heart when transposition exists.

Dorning (1890) reported the occurrence in a boy 8½ years old of a *bona fide* example of complete transposition of the great vessels with unusually long survival

CORRECTED TRANSPOSITION OF THE GREAT VESSELS

Corrected transposition of the great vessels is a rare and peculiar type of malformation. The aorta and pulmonary trunk are related to each other as in complete transposition of the great vessels, the aorta lying ventral to the pulmonary trunk and the two vessels running parallel to each other In spite of this arrangement, the aorta arises from the left ventricle and the pulmonary trunk from the right ventricle. The venous connections with the heart are normal, so that the peculiar relationship of the great arteries is in itself of no functional consequence to the patient, and many patients with this defect live to adult life.

Walmsley (1931) reported an instance of this defect in a man aged 25 years who died of cardiac failure He pointed out that the right atrioventricular valve has the appearance of the normal mitral valve and the left atrioventricular valve the characteristics of the normal tricuspid valve The right atrioventricular valve is related to the transposed pulmonary valve as is the normal mitral valve to the aortic valve The musculature of the left ventricle in corrected transposition of the great vessels resembles that of the normal right ventricle in being highly trabeculated; the right ventricle has the characteristics of the normal left ventricle. Walmsley stated

that up to 1923 there had been 16 reported examples of this malformation and that a ventricular septal defect was present in every instance

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TABLE V-2
Manner in Which Truncus Arose from Ventricular Part of Heart in 60 Cases of Persistent Truncus Arteriosus Classified by Collett and Edwards (1949) According to the Four Types of the Malformation in Their Classification (*Reproduced by Permission of the W B Saunders Co*)

Origin of Truncus	*Number of Cases*				
	Type 1	*Type 2*	*Type 3*	*Type 4*	*Total*
From both ventricles (overriding septal defect)	17	11	3	7	38
From right ventricle	7	3	4	2	16
From left ventricle	2	0	0	0	2
From single ventricle	8	9	2	0	19
Unknown	4	0	0	1	5

V-2) The four types were subdivided according to the direction of the aortic arch and the presence or absence of the ductus arteriosus. The characteristics of the four major types follow.

Type 1. A single pulmonary trunk and the ascending aorta arise from the truncus arteriosus (Figure V-37*a*).

Type 2. The right and left pulmonary arteries arise close together from the dorsal wall of the truncus arteriosus (Figure V-37*b*).

Type 3. One or both pulmonary arteries arise independently from either side of the truncus arteriosus (Figure V-37*c*).

Type 4. The pulmonary arteries and the ductus arteriosus are absent The sixth aortic arches are apparently absent. The arterial circulation to the lungs is furnished by the bronchial arteries (Figure V-37*d*)

Type 1. Type 1 was represented by 38 cases which are subdivided according to seven different anatomic variations. In each case a short pulmonary trunk and ascending aorta arose from the truncus arteriosus (Figure V-38) The first subdivision comprised 21 cases in which the aortic arch turned to the left, the ductus

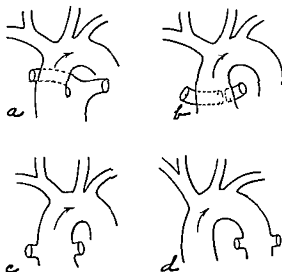


Figure V-37 The four types of persistent truncus arteriosus *a* Type 1. *b* Type 2 *c* Type 3 *d* Type 4 (From Collett and Edwards. Reproduced by permission of the W B. Saunders Co)



Figure V-38 Persistent truncus arteriosus, Type 1. The right ventricle has been opened showing the origin of the persistent truncus arteriosus from both ventricles above a septal defect A short pulmonary trunk gives rise to the right and left pulmonary arteries (From Dry and associates Reproduced by permission of *Postgraduate Medicine.*)

arteriosus was absent and the pulmonary trunk sprang from the left side of the truncus arteriosus. This subtype represented the largest single group of cases of the series. The second subtype differed from the first in that the pulmonary trunk arose from the right side of the truncus arteriosus. There were five cases of this subtype. The third subtype, represented by three cases, differed from the first only in that the ductus arteriosus was present.

There was only one case each of the fourth and fifth subtypes but they were closely related. The example of the fourth subtype was reported by Feller (1931) and consisted of an associated coarctation of the aorta between the origin of the left common carotid and the left subclavian arteries In the case of the fifth subtype, reported by Preisz (1890), there was complete interruption of the aorta at approximately the same site as the coarctation in the former case. In each instance the ductus arteriosus carried blood to the descending aorta. The sixth subtype was represented by six cases, and in these the pulmonary trunk arose from the left side of the truncus arteriosus but the aortic arch was on the right side.

In the last case of Type 1, representing the seventh subtype, there was a double aortic arch, and the pulmonary trunk arose from the left side of the truncus arteriosus.

Type 2. Twenty-three cases were encountered of Type 2 They were subdivided into four anatomic subtypes in the same manner as the first four subtypes of Type 1. In all of these cases both the right and left pulmonary arteries arose directly from the posterior aspect of the truncus, their orifices being very close to each other. The 18 cases of the first subtype were comparable to those of the first subtype of Type 1 in that the aortic arch was on the left and there was no ductus arteriosus. Only two cases were of the second subtype. In these the ductus arteriosus was present and the aortic arch was normal. The case reported by Tiedemann (1831) representing the third subtype of Type 2 was similar, with respect to the structure of the aortic arch, to Case 16 of Preisz (1890). The aortic arch was completely interrupted. In the two remaining cases of Type 2, a right aortic arch was present.

Type 3. Nine cases were classified as Type 3. They were divided into four anatomic subtypes. The pulmonary arteries arose independently from the right and left lateral walls of the truncus arteriosus. The first subtype was represented by four cases in which the aortic arch was on the left and the ductus arteriosus was absent. In cases of the second and fourth subtypes, only one pulmonary artery was present and it supplied only one lung, the contralateral lung was supplied by enlarged bronchial arteries or a persistent ductus arteriosus. These two subtypes differed from each other in the direction of the aortic arch. The one case of the third subtype was reported by Mallory and associates (1948). They stated that the fifth aortic arches were persistent. More logically, it seems that this case is comparable to those in the first subtype of Type 3 except for the right-sided aortic arch, the defect resembling a mirror image of this subtype.

Type 4. The cases of Type 4 were those in which the right and left pulmonary arteries, the pulmonary trunk and the ductus arteriosus were absent. The lungs were supplied solely by bronchial arteries arising either from the arch of the aorta or from the descending aorta. There were 10 cases of this type, which were subdivided into four subtypes The first subtype was represented by seven cases; in all of these there was a left aortic arch and the bronchial arteries arose from the descending

aorta. Each of the remaining three subtypes was represented by one case

The case of Gallois (1896) of the second subtype and the case of Graham and Montgomery (1938) of the third subtype each had a left aortic arch. They differed from each other only in the location of origin and in the number of bronchial arteries. In the first case reported by Siegmund (1928), representing the fourth subtype, a right aortic arch was present and the bronchial arteries arose from the descending aorta.

Simultaneous with the appearance of the communication by Collett and myself was the paper by Manhoff and Howe (1949) The latter contained a comprehensive discussion on the subject of persistent truncus arteriosus In addition they reported a case which, according to our classification, would be designated as persistent truncus arteriosus, Type 4. They indicated, however, that their case should not be considered as an example of persistent truncus arteriosus, although similar cases reported earlier had been so designated They preferred to introduce a new designation for the condition, namely, "*absence of the pulmonary artery.*" They argued correctly that the absence of the right and left pulmonary arteries must be considered as indicating either absence or early involution of the sixth aortic arches. They argued further that the failure of the embryonic truncus arteriosus to be partitioned into pulmonary trunk and aorta was secondary to this deficiency of the sixth aortic arches The second interpretation, however, need not be correct. It is also possible that the absence of the sixth aortic arches and the failure of the truncus arteriosus to be partitioned were two independent conditions. Manhoff and Howe considered that in their case the truncus arteriosus had failed to be partitioned. Any other view is inescapable. Yet they prefer to designate the single vessel leaving the heart as the aorta rather than a truncus arteriosus. That this vessel has the gross anatomic characteristics of the aorta cannot be denied, but from a developmental point of view it is the same unaltered vessel as the embryonic truncus arteriosus. In my opinion this case must be considered to be a form of persistent truncus arteriosus

In addition to the 80 cases of persistent truncus arteriosus classified by Collett and me, 11 cases which seemed to be examples of this malformation lacked adequate data on the arterial supply to the lungs to permit classification.

In persistent truncus arteriosus *the ventricular septum is defective* As a rule the defect involved only the membranous portion, but in almost one-fourth of the cases there was complete absence of the muscular portion of the septum as well, the heart exhibiting the characteristics either of *cor biloculare* or *cor triloculare biatriatum.*

The truncus arteriosus usually arises from both ventricles superior to the ventricular septal defect but occasionally it arises from the right ventricle exclusively. Less often the truncus arises from the left ventricle alone The manner in which the truncus arose from the ventricular part of the heart in 80 cases of malformation classified by Collett and me is summarized in Table V-2.

The number of cusps in the semilunar valve of the truncus has been the subject of considerable discussion Humphreys (1932) has been a leading advocate in requiring the existence of four cusps in making the diagnosis of persistent truncus arteriosus. This criterion for morphologic diagnosis does not seem essential and gains little support from the developmental characteristics of the malformation. Among the reports of the 80 cases which Collett and I classified there were data as to the number of valve cusps in 60 of the cases. In the majority (43 cases) the valve of

truncus was formed by three cusps In nine cases, each of which was an example of our Type 1, there were four cusps. Six cases exhibited three cusps, one of which was partially separated into two. In one case there were six cusps and in another case the valve was bicuspid.

The coronary arteries arise from the truncus arteriosus In an unusual instance there is departure from the standard picture of two coronary arteries In one case there were three coronary arteries and in seven cases a single coronary artery.

The aortic arch is rather frequently anomalous In 80 cases of persistent truncus arteriosus a right aortic arch was present 11 times, and a double aortic arch was present once (Kerwin, 1936). In the other 68 cases of persistent truncus arteriosus the aortic arch was either described as being, or was assumed to be, on the left side.

Absence of the ductus arteriosus is common in persistent truncus arteriosus, the ductus being absent in more than half of the cases. In cases of Type 4, by definition, the ductus is always absent. In this type the sixth aortic arches, from one of which the ductus arteriosus is derived, have failed to form. In the other three types of truncus arteriosus the frequent absence of the ductus arteriosus is understandable for yet another reason. In the normal fetus the ductus arteriosus may be said to have a safety-valve mechanism. That blood that flows from the right side of the heart and not to the lungs is carried through the ductus arteriosus into the descending aorta. In persistence of the truncus arteriosus there is of course no effective partition between the pulmonary arterial and aortic channels. In this way the blood that leaves the heart and does not go to the lungs is readily carried to the aorta at the level where this vessel arises from the truncus arteriosus. The ductus arteriosus is evidently used little as a safety-valve channel and, as the right ductus arteriosus disappears in the normal fetus, the left may also disappear in the fetus with a persistent truncus arteriosus. Evidently the ductus arteriosus may disappear so early during fetal life that by the time of birth it no longer can be recognized as a distinct structure.

Absence of the ductus arteriosus is not peculiar to persistent truncus arteriosus although this phenomenon occurs more often in this malformation than in other types of congenital cardiac anomalies. The ductus arteriosus may be absent in the tetralogy of Fallot, in cases with a single ventricle and occasionally in instances of ventricular septal defect. In each of these conditions the malformation allows sufficient communication between the two circulations during fetal life so that the ductus is used little and may, therefore, undergo atrophy.

Incorrect Interpretation of Persistent Truncus Arteriosus

Of the 116 cases which Collett and the author reviewed there were 12 which, although considered by some to be examples of persistent truncus arteriosus, did not seem to be *bona fide* examples of this condition. The characteristics of these cases were (1) origin from the heart of a single arterial trunk which followed the course of the aorta and (2) origin of the pulmonary arterial system from a ductus arteriosus. In eight of these cases two pulmonary arteries arose from a patent ductus arteriosus. We excluded such cases from the designation of persistent truncus arteriosus for the following reasons: Since the right and left pulmonary arteries are derived from the proximal portions of the right and left sixth aortic arches, the presence of both of them presupposes that the proximal portions of the right and left sixth aortic arches were present at one time; since the right and left pulmonary

arteries showed no connection with the truncus or a derivative of it, those parts of the sixth arches must have been present at one time but must have subsequently disappeared. Under these circumstances it is impossible to state whether the sixth aortic arches had arisen from a truncus arteriosus or from a pulmonary trunk which had developed from partitioning of the truncus. There are numerous instances in the literature which resemble these eight cases in that the pulmonary blood supply is obtained through a ductus arteriosus, although an atretic pulmonary trunk is present, as illustrated in Figure V-18*c* and V-18*d*. Inasmuch as it is impossible to determine in these eight cases whether or not the truncus had in fact been partitioned at one time, it is impossible to include these cases unequivocally as examples of persistent truncus arteriosus. This view is shared by Manhoff and Howe

In the case of a right aortic arch reported by Harris (1926) there was absence of the left lung. The arterial supply to the right lung appeared to be by way of a right-sided ductus arteriosus Thus interpreted, a right-sided pulmonary artery might have developed at one time but subsequently disappeared.

In three cases a single arterial vessel arose from the heart but the pulmonary arterial supply arose from a right-sided ductus arteriosus connecting with the innominate artery (Herxheimer, 1910; Wood and Williams, 1928, Mehta and Hewlett, 1945)

The type of case under discussion is removed from the category of persistent truncus arteriosus, since there is reason to believe that the truncus arteriosus had been partitioned but as a result of abnormality in this process the pulmonary trunk is so small as to escape detection This type of case may be considered to exhibit the severest degree of pulmonary stenosis. When it is viewed in this light and when consideration is given to the other abnormalities in the heart, it seems proper to apply the diagnosis of tetralogy of Fallot to these cases The designation "pseudotruncus arteriosus" for such cases is currently employed by Dr. Helen Taussig (see Tetralogy of Fallot), although in her paper on the clinical characteristics of persistent truncus arteriosus (1947a) and in her monograph (1947b) such cases were designated as "truncus arteriosus." It is realized that, while these cases cannot be accepted as examples of persistent truncus arteriosus from a developmental point of view, they function exactly as do instances of persistent truncus arteriosus, Type 4.

Functional Disturbances

Persistent truncus arteriosus exemplifies the maxim that certain malformations with the same anatomic designation may function less like each other than like malformations with quite different anatomic arrangements In persistent truncus arteriosus Type 1 the pulmonary arteries are usually wide There is no problem of pulmonary stenosis. The ejectile ventricular force is common to the pulmonary and the systemic circulations For these reasons this form of persistent truncus arteriosus is functionally like the Eisenmenger complex. Although no comprehensive study on the structure of the intrapulmonary arteries of this condition has been reported, it is expected that a study of appropriate cases would reveal the same changes in the intrapulmonary arteries as are seen in the Eisenmenger complex. Pulmonary hypertension is an expected finding in Type 1 As the functional characteristics of Type 1 may be compared to those of the Eisenmenger complex, so Type 4 may be compared to the tetralogy of Fallot with pulmonary atresia. In Type 4, in which no pulmonary arteries exist and the pulmonary arterial supply is dependent on

eral arteries, the absence of the pulmonary arteries is responsible for the same functional effect as if pulmonary arteries were present anatomically but with atresia at one region or another.

Continuing with the comparison of the types of persistent truncus arteriosus with the tetralogy of Fallot and with the Eisenmenger complex, Types 2 and 3 will vary from case to case. Those in which the pulmonary arteries are wide are to be compared functionally with the Eisenmenger complex, while those in which the pulmonary arteries are narrow function like the tetralogy of Fallot In each of the four types there is a venous-arterial and an arteriovenous shunt

Incidence, Survival and Complications

Persistent truncus arteriosus is relatively uncommon In the 212 cases of malformations of the heart and great vessels in the Mayo Clinic pathologic collection there are three examples of this condition. Each is an example of the Type 1 form of this malformation. In one case, which was reported by Beaver (1933), the patient was a newborn infant. A second patient died when one month of age, and the third, whose data were presented in the clinicopathologic analysis of Dry and associates (1948), died at the age of eight months.

The outlook as regards life expectancy in patients who have persistent truncus arteriosus is poor. Table V-3 presents a summary of the age at death in the 80 cases of persistent truncus arteriosus which Collett and the author classified. Of the 74 patients on whom data as to age were given, only one of the 34 patients with Type 1 lived 10 years or longer. In Type 2, four of 22 patients lived 10 years or longer, the oldest patient of the eight with Type 3 was 14 months of age at the time of death. The longest average survival occurred in Type 4, of 10 patients with this form, five lived 10 years or longer, and three of these five lived for 20 or more years.

TABLE V-3

Age at Time of Death of Patients with Persistent Truncus Arteriosus Modified from Collett and Edwards (*Published by Permission of W. B Saunders Co.*)

Age at Death	*Total*	*No of Cases of Persistent Truncus Arteriosus, According to Type*			
		Type 1	*Type 2*	*Type 3*	*Type 4*
Stillborn to 7 days	25	11	10	3	1
8 days to 6 mos.	29	17	7	2	3
7 to 14 mos	7	3	1	3	0
15 mos to 9 yrs.	3	2	0	0	1
10 to 19 yrs.	5	1	2	0	2
20 yrs. or more	5	0	2	0	3
Age not given	6	4	1	1	0
Totals	80	38	23	9	10
Range of ages		(1 hr. to 13 yrs)	(stillborn to 36 yrs)	(1 hr to 14 mos)	(1 hr to 33 yrs)

A case of Ramsbotham (1829), which may be classified as persistent truncus arteriosus, Type 4, and the case of Manhoff and Howe, which was similar, were not included in our review. Ramsbotham's patient died of pulmonary tuberculosis at the age of 16 years, and Manhoff and Howe's patient died of pneumonia at the age of 10 months

In most instances of persistent truncus arteriosus death is related to the malformation. In some cases this is probably brought about by hypoxia, to which pneumonia at times contributes. In the cases of Type 1 it is possible that death is related to excessive rather than deficient pulmonary blood flow.

Bacterial endocarditis is a rare complication, probably because many of the patients die at an early age from other causes. Only one example of this complication was encountered (Solis-Cohen *et al.*,

1944) The patient was a girl aged eight years in whom the malformation was characterized by absence of the pulmonary arteries and blood was supplied to the lungs by bronchial arteries. The bacterial endocarditis originated on the tricuspid valve. Two examples were encountered of cerebral abscess complicating persistent truncus arteriosus (Hulse, 1918, Greenspon and Leaman, 1939).

Partial Persistent Truncus Arteriosus (Congenital Communication Between Aorta and Pulmonary Trunk; Congenital Aortic Septal Defect)

There is an interesting group of cases which may seem at first not to meet the required criteria for the diagnosis of persistent truncus arteriosus These are cases in which the pulmonary and aortic channels are separated at the level of the semilunar valves, and the ventricular septum is usually intact, but a localized defect in the septal system superior to the semilunar valves produces a communication between the ascending aorta and the pulmonary trunk (Figure V-39).

The localized defect is due either to absence of development of the truncoconal septum at the level of the defect or to localized fenestration of the septum after it has formed Rarely there may be a large defect between the pulmonary trunk and the aorta even though their respective semilunar valves are well formed and the ventricular septum is intact.

Since persisent truncus arteriosus, defined on a developmental basis, is manifested by incomplete division of the truncoconal channel by the truncoconal septum, these cases represent partial persistence of the truncus arteriosus They were so designated by Collett and me but it is to be emphasized that the condition functions quite differently from the fully developed forms of persistent truncus arteriosus Whereas in each of the four types of persistent truncus arteriosus there is both a venous-arterial and an arteriovenous shunt, in partial persistent truncus arteriosus there is usually only an arteriovenous shunt, the cases being comparable from a functional viewpoint to patent ductus arteriosus Potts and associates (1949) reported on two cases with clinical signs which were suggestive of, but somewhat atypical for, patent ductus arteriosus. At operation it was felt by the authors that the malformation was characterized by a communication between the ascending aorta and the pulmonary trunk.

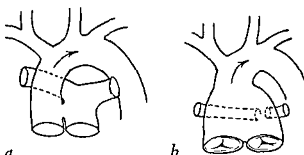


Figure V-39 *a* Partial persistent truncus arteriosus (congenital communication between ascending aorta and pulmonary trunk) *b* Partial persistent truncus arteriosus with a large communication as in the cases of Bain and Parkinson (1943) and of Dadds and Hoyle (1949)

Perelman and Putschar (1949) have stressed that when dealing with the specimen it may be difficult or impossible to be certain whether the communication is congenital or acquired. This is particularly

true when the communication is encountered in an adult and when there is an inflammatory process at the margins of the communication These authors also emphasized that the communication is supravalvular and proximal to the location of the ductus arteriosus. At times a patent ductus arteriosus may be so short that the walls of the aorta and the left pulmonary artery are in apposition, – the so-called window type of patent ductus arteriosus. The aortic mouth of such a communication lies beyond the origin of the left subclavian artery and so is removed in location from that part of the aorta involved in the communication under discussion.

Perelman and Putschar reviewed 13 reported cases of communication between the ascending aorta and the pulmonary trunk and reported an instance of this defect which they had observed in a newborn infant. While some of the patients died during infancy, five of the 13 lived to adult life, the oldest being 48 years at the time of death Congestive cardiac failure was the cause of death in the older patients and in some of the children. Twelve of the 13 cases reviewed by Perelman and Putschar coincide with 12 of the 13 cases of partial persistent truncus arteriosus which Collett and the author reviewed. The case of Oberwinter (1904), of a man 40 years old, was not included in our review. The case of Bain and Parkinson (1943) reviewed by us was not listed by Perelman and Putschar. The latter case is of special interest since, as in the case reported by Hektoen (1899), the communication between the aorta and the pulmonary trunk was much more extensive than in the other cases The patient of Bain and Parkinson was a young man aged 18 years. Above the cardiac ventricles there was an ovoid aneurysmal sac, measuring 8 cm. in greatest dimension The sac had six apertures. One orifice led to an arterial trunk from which arose the innominate, the left common carotid and left subclavian arteries; the second aperture led to the descending aorta, the third and fourth were dorsal and represented the ostia of the right and left pulmonary arteries, the fifth and sixth were caudal and communicated with the base of the aorta and of the pulmonary trunk. The aortic and pulmonary orifices were properly formed and each contained its respective valve. The ventricular septum had no defect. The case of Dadds and Hoyle (1949), in which the patient was a boy aged 15 years who died of congestive cardiac failure, was similar to that of Bain and Parkinson. The pulmonary trunk was dilated to aneurysmal proportions and there was a large communication with smooth edges between the ascending aorta and the pulmonary trunk. The defect measured 6 x 5 cm. in diameter. The ventricular septum was intact and the aortic and pulmonary valves were normally formed. This case was not listed in either the review of Perelman and Putschar or that of Collett and me.

In our discussion Collett and I mentioned several cases in which there was a communication between an aortic sinus and the right ventricle. While we implied that such cases might represent forms of partial persistent truncus arteriosus, my present feeling is that such cases represent, not malformations of the truncoconal septal system, but rather malformations of the coronary arteries. Such communications are discussed in greater detail in the section on Malformations of the Coronary Arteries in this chapter.

Developmental Basis for Malformations

Many have been tempted to supply or refer to theories, such as Spitzer's phylogenetic theory, in order to explain the developmental basis of the malformations resulting from abnormalities in partitioning of the truncus and conus arteriosus. This

does not seem logical. While it is of interest to compare the human heart containing malformations with the normal heart of lower forms, some stages of the developing human heart and of the hearts of lower animals are not comparable.

While certain malformations of the human heart may be readily explained on the basis of arrested development at some stage in the formation of the heart, most of the malformations which are discussed in this section do not represent such an arrest in development. It becomes necessary to theorize not only on the stage in cardiac development in which the abnormality started but also on the basic abnormality in the developmental process leading to the malformation. It is to be emphasized that many of the explanations given, even with the employment of human embryology as a basis, may require revision when new facts concerning development are discovered.

To gain some insight into the possible cause for those malformations characterized by abnormal arterioventricular connection one must have an understanding of the normal process by which the embryonic truncoconal channel becomes partitioned into two vessels of about equal size and of the influence of the partitioning process in making the aorta communicate exclusively with the left ventricle, and the pulmonary trunk with the right ventricle. These matters are described in Chapter II. If the truncoconal ridges are located eccentrically, the septum formed by their fusion will be asymmetrically placed and the truncoconal channel will be partitioned unequally. This seems to be the essential abnormality leading to the development of the complex of malformations known as the *tetralogy of Fallot.* In this condition the unequal division of the truncoconal channel is such as to create an abnormally narrow pulmonary trunk and a correspondingly wide aorta This displacement of the truncoconal septum interferes with one of the three components involved in the formation of the membranous portion of the interventricular septum It will be recalled that in order for this part of the septum to be completed it is essential that the inferior aspect of the truncoconal septum be in line with the superior portion of the main muscular part of the ventricular septum. If, as in this condition, the truncoconal septum is eccentric, it is out of line with the main muscular part of the ventricular septum and so cannot join with it to make its contribution to the membranous septum. The result is a membranous septal defect

The fact that the large aorta in part overlies the right ventricle may be due merely to its disproportionate size which makes it trespass on what is normally pulmonary territory There may also be some degree of abnormal position of the aorta due to abnormal spiraling of the truncus septum.

In the *Eisenmenger complex* there seems to have been little in the way of abnormality of the partitioning of the truncus arteriosus, since the two great arteries rotate about each other in a normal manner after they have ascended from the heart In the lower part of the truncoconal channel there seems to have been a deficiency of the septum. This would be responsible for the failure of the aorta to communicate exclusively with the left ventricle, and the same deficiency would explain the presence of a ventricular septal defect.

The developmental basis for the *Taussig-Bing complex* might be explained as follows· With failure of spiraling of the lower part of the truncoconal septum the aorta would gain connection with the right ventricle It would seem that in this malformation little, if any, spiraling of the inferior part of the truncoconal septum had taken place. This would also explain the biventricular communication of the pul-

monary trunk as well as the membranous defect of the ventricular septum.

The appearance of the great vessels in *complete transposition of the great vessels* suggests that the embryonic truncus arteriosus had been partitioned by a septum which spiraled little if at all and that the plane of the septum was placed in a right-to-left position. In this way the aorta comes to lie ventral to the pulmonary trunk and communicates with the right ventricle. With the truncoconal septum so far removed from a normal position it would be expected that a membranous ventricular septal defect would be a constant feature in this condition. In the text on this malformation it was pointed out, however, that the ventricular septum may have no defect. When this happens, the ventricular septum seems to be entirely muscular, so that the membranous portion may be said to be absent and the interventricular foramen closed by an anomalous bundle of muscle

Persistent truncus arteriosus seems to be a clear example of a developmental arrest in which the truncoconal septum fails to form completely. The truncus and conus arteriosus maintain their embryonic condition of representing a single arterial channel leaving the ventricular part of the heart In persistent truncus arteriosus of Type 1 there is a short pulmonary trunk. This is interpreted as representing minimal partitioning of the superior part of the truncus arteriosus while the remainder of the truncoconal channel remains unpartitioned.

The partitioning of the truncus arteriosus begins at about the fifth week of intrauterine life, and the ventricular septum is completely formed by the end of the eighth week (Chapter II). The malformations considered to result from abnormalities in the partitioning of the truncus and conus arteriosus, namely, the tetralogy of Fallot, the Eisenmenger complex, the Taussig-Bing complex, complete transposition of the great vessels and persistent truncus arteriosus, probably originate during this crucial period of four weeks.

Stenosis of ostium infundibuli is probably logically classed with the malformations of the truncus and conus arteriosus. While strictly speaking it does not seem to result from an abnormality in the partitioning of the truncoconal channel, it is probably caused by faulty molding of the outflow part of the heart with the sinus portion, as suggested by Keith.

There is considerable discussion as to whether *subaortic stenosis* should be considered a congenital malformation. The opinion of the author is that the fibrous component of the condition is probably acquired, but that the peculiar bulge of the ventricular septum into the outflow tract of the left ventricle and the deviation of the aorta to the right are congenital malformations. The latter seem to be the basic cause of the difficulty. By being placed as it is, the prominent ventricular septum itself acts to narrow the outflow tract. The formation of fibrous tissue is probably a reaction to the trauma of the stream of outflowing blood striking the narrowed portion of the subaortic region. A like opinion was expressed by Greenberg and Simon (1949). This opinion is not at variance with the opinion of Keith (1909) who explained subaortic stenosis as follows: That part of the heart from which the infundibulum is derived, the bulbus cordis, normally disappears completely from the left side of the heart but a trace of it may persist, giving rise to subaortic stenosis. If we accept Keith's explanation, we would interpret the muscular bulging into the left ventricular outlet as representing persistence of the bulbus cordis. The interpretation that the fibrous ring is acquired is not inconsistent with the hypothesis of Keith.

DEXTROCARDIA

Lichtman (1931), who made an extensive review of the literature on dextrocardia, gave the following *definition* Dextrocardia is characterized by the heart assuming a position in the right side of the thorax with the apex pointing to the right The basis is a congenital malformation of the heart. Excluded from the category of dextrocardia are those cases in which the heart is on the right by virtue of congenital or acquired disease in neighboring structures *Isolated dextrocardia* is defined as dextrocardia in association with normal position of all the other viscera In their communication on new aids in the diagnosis of dextrocardia, Chapman and Gibbons (1950) used the *classification* on dextrocardia of Mandelstamm and Reinberg. This classification includes three types. The first type is associated with complete or partial situs inversus of other viscera The second and third types are each examples of isolated dextrocardia. In the second type, the cardiac chambers show mirrored inversion, the arterial chambers being on the right and the venous chambers on the left In the third type the cardiac chambers show a normal relationship, the venous chambers being on the right and the arterial chambers on the left. After an extensive review of the literature, Rosler (1930) concluded that isolated dextrocardia is always *associated with cardiac malformations* Lichtman was of the same general opinion but he stated that in his review of 161 cases of isolated dextrocardia there were three with no isolated cardiac defect.

Brown (1939) referred to a case of Stevenson in which there was likewise no malformation associated with the isolated dextrocardia. Even in the dextrocardia of situs inversus, cardiac malformations are common (Taussig, 1947). The malformations which are associated with isolated dextrocardia frequently include pulmonary stenosis. Septal defects are also often present. It is to be emphasized that it is difficult to categorize an exact type of malformation associated with isolated dextrocardia since a variety of intricate deformities of the heart may be associated with isolated dextrocardia

In the case of isolated dextrocardia illustrated by Dry and associates (1948), the patient, a female infant 10 months old, had a single ventricle. Inasmuch as congenital malformations of the heart are common in cases of isolated dextrocardia, life expectancy is often short. The average age at death is less than 30 years, many of the patients dying during the first year of life.

An exceptional case is that of Ruskin and associates (1943). Their patient was a woman who was 55 years of age when she was studied clinically She had had seven pregnancies.

Transposition of the great vessels is commonly associated with isolated dextrocardia, in some cases of which the *transposition is corrected* The aortic arch may cross ventral to the right bronchus, but usually it crosses over the left The descending aorta usually is on the left side, regardless of the position of the aortic arch The electrocardiographic features of isolated dextrocardia have been reviewed by Shepard and Stewart (1948) and by Burchell (1949)

Isolated levocardia or *isolated sinistrocardia* is characterized by the heart and apex pointing to the left in patients with situs inversus. In these cases congenital malformations of the heart are probably as common as are malformations in patients with isolated dextrocardia

One example of such a condition is present in the Mayo Clinic pathologic collection. This specimen was derived from a male infant six months of age with situs inversus. In this patient the venous atrium

and ventricle were on the left and the arterial atrium and ventricle on the right. The great vessels were transposed so that the aorta arose from the right (arterial) ventricle. The orifice of the pulmonary trunk, which exhibited valvular atresia, straddled a ventricular septal defect The aortic arch was on the right as were the descending aorta and the patent ductus arteriosus. There were two superior venae cavae, the left entering the left-sided (venous) atrium in a manner similar to the entrance of the superior vena cava into the right atrium of normal persons. The right superior vena cava joined the right extremity of the coronary sinus to produce a mirror image of persistent left superior vena cava in persons with normally disposed organs The coronary sinus entered the left-sided (venous) atrium.

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Congenital Malformations

D. Malformations of the Valves

MALFORMATIONS OF THE ATRIOVENTRICULAR VALVES

Persistent Interatrial Foramen Primum with Common Atrioventricular Canal

Less common than defects occurring in the region of the foramen ovale are those which involve the inferior portion of the atrial septum. On the basis of the developmental origin of defects of the lower part of the atrial septum, the explanation of which is to follow, such defects may be considered to represent persistence of the embryonic interatrial foramen primum. Usually such septal defects are associated with serious abnormalities of the atrioventricular valves.

In persistent interatrial foramen primum the atrial septal defect has a characteristic appearance. It is crescent-shaped and involves the most inferior portion of the recognizable atrial septum. The defect overhangs the atrioventricular region (Abbott, 1924; Abbott and Kaufman, 1910; Gunn and Dieckmann, 1927; Monckeberg, 1923, Moragues, 1943, Peacock, 1846, Robinson, 1941; Robson, 1931). When the heart is dissected in a routine manner, the examiner is impressed with the fact that the anterior or aortic leaflet of the mitral valve and the septal leaflet of the tricuspid valve are each split into an anterior half and a posterior half (Figures V-40*a* and V-40*b*). When more care is given to the interpretation of the valvular changes, it becomes apparent that instead of a mitral valve and a tricuspid valve being present, there is but one atrioventricular valve, which is common to both sides of the heart (Figure V-41). What had been interpreted as the anterior halves of the split leaflets of the mitral and tricuspid valves is in reality a common anterior leaflet of a common atrioventricular valve. Likewise the posterior halves of the split leaflets are continuous and in reality form a posterior leaflet of the common valve. Usually there are two lateral leaflets on the right side representing the

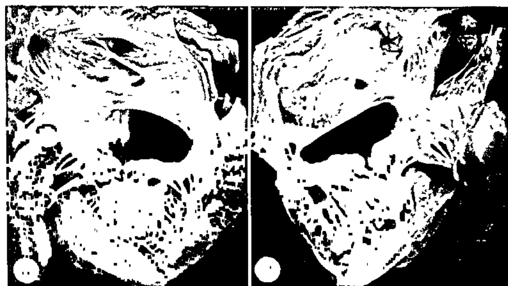


Figure V-40 Patent interatrial foramen primum with common atrioventricular canal in a female infant two and one-half months old (From Rogers and Edwards, 1948 Reproduced by permission of the C V Mosby Company)

a The left side of the heart Above the cleft aortic leaflet of the mitral valve is a crescent-shaped defect in the inferior part of the atrial septum The latter represents persistence of interatrial foramen primum Above this, the foramen ovale shows a slight degree of patency on the basis of a short valve of the foramen ovale The chordae tendineae of the ventral half of the cleft aortic leaflet of the mitral valve are inserted into the anterior papillary muscle of the left ventricle Some of the chordae of the posterior half of the leaflet are inserted into the ventricular septum

b The right side of the heart The septal leaflet of the tricuspid valve shows a cleft similar to that in the aortic leaflet of the mitral valve shown in *a* The lower limbus of the fossa ovalis is deficient The defect in the inferior part of the atrial septum and the patent foramen ovale which were seen in *a* are shown Right atrial dilatation and a right ventricular hypertrophy are present

elements which normally form the anterior and posterior tricuspid leaflets On the left side the common valve has a lateral leaflet, which in turn is the counterpart of the posterior mitral leaflet of normal hearts Shaner (1949) has observed this malformation in pig embryos.

The chordae tendineae of the anterior common leaflet are attached to two different regions. Those attached to the left side of the valve insert into the anterior papillary muscle of the left ventricle while those attached to the right side of the leaflet are inserted into a corresponding papillary muscle in the right ventricle (Figure V-40). The chordae tendineae of the common posterior leaflet are usually short Some are attached to the crest of the underlying muscular ventricular septum and to adjacent portions of the respective sides of the septum in each ventricle or to papillary muscles The chordae of the lateral leaflets are attached to papillary muscles corresponding to those to which the anterior and posterior tricuspid leaflets and the posterior mitral leaflets attach normally. It is to be emphasized that the shortness of the posterior common leaflet, together with the presence of chordae that are usually quite short, is probably responsible for insufficiency of the valve during life

If the malformation under discussion occurs in a less developed form than that described, the same type of defect of the inferior part of the atrial septum exists but there is evidence of incomplete partitioning of the embryonic common atrioventricular canal (Sternberg, 1913). In such hearts the tricuspid valve is usually

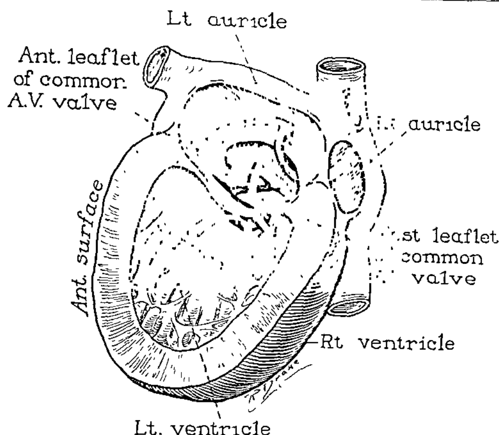


Figure V-41
Rogers and Ec
lateral walls of
common to both sides of the heart It is guarded by a single valve possessing large anterior and posterior leaflets, two right lateral leaflets and a left lateral one The interatrial foramen primum is patent, as is the posterior upper portion of the ventricular septum

fairly well formed but the mitral valve is abnormal (Figure V-42). Its anterior leaflet shows a cleft involving all of the leaflet except its base. The ventricular septum is not defective

Rokitansky (1875) described two groups of hearts with cleft atrioventricular valves and defects in the inferior portion of the atrial septum. In one group, there was an associated defect of the superoposterior portion of the ventricular septum, and in the other group, the ventricular septum was not defective. Schmaltz (1888) in a discussion of Rokitansky's classification of these two groups of hearts expressed the opinion that the distinction was artificial Nevertheless, Abbott (1936) essentially maintained the grouping of Rokitansky Instances in which the heart had no defect in the ventricular septum were classified as *persistent ostium primum with cleft mitral valve*, and those with an added defect of the ventricular septum were classified as *persistent common atrioventricular ostium*, or "*incomplete double heart.*" The author agrees with Schmaltz that the separation of these cases into two groups is artificial. In recalling the embryologic features of the defects under discussion, it is evident that the cleft of the aortic leaflet of the mitral valve and of the septal leaflet of the tricuspid valve represents persistence of the common atrioventricular canal and is the crucial point in classifying these



Figure V-42. Patent interatrial foramen primum with partial persistence of the common atrioventricular canal in a male infant six months old (From Rogers and Edwards, 1948. Reproduced by permission of the C V Mosby Company.)

a The heart viewed from the right In the inferior part of the atrial septum there is a crescent-shaped defect characteristic of persistent patency of interatrial foramen primum The tricuspid valve is essentially normal In the region of the foramen ovale there is a large defect. The limbus of the fossa ovalis is not identifiable.

b Beneath the defect in the inferior part of the atrial septum the aortic leaflet of the mitral valve is cleft except at its very base The additional defect of the atrial septum, in the region of the foramen ovale, is also shown





foramen primum in a male infant d from the right

Company.)

b Patent interatrial foramen primum with common atrioventricular canal in a female infant five months old The heart is viewed from the left. Beneath the defect in the lower part of the atrial septum, the aortic leaflet of the mitral valve is cleft. Beneath the valve there is a small defect in the ventricular septum. (From Rogers and Edwards, 1948 Reproduced by permission of the C. V. Mosby Company.)

cases. A defect in the inferior part of the atrial septum, while not necessary for the diagnosis, is practically always associated with persistence of the common atrioventricular canal and undoubtedly represents failure of union of the ventral and dorsal atrioventricular endocardial cushions with the septum primum. On the other hand, a defect of the posterior portion of the ventricular septum is not always present, nor need it be, since the ventricular septum does not take part in dividing the primitive atrioventricular canal into right and left halves. The foramen ovale may be normally formed (Figure V-43*a*) or there may be several types of abnormalities in the region. In some cases the foramen ovale is patent, as in those cases in which patency of the foramen ovale is the sole malformation (Figures V-40 and V-42) In other instances the inferior part of the limbus of the fossa ovalis may be absent (Figure V-40).

It is evident that the anatomic arrangements in persistent interatrial foramen primum with common atrioventricular valve may allow a considerable amount of oxygenated blood to be shunted from the left side of the heart into the right atrium. The mere presence of an atrial septal defect would allow such a shunt. To this is added the effect of regurgitation through the common atrioventricular valve Thus during ventricular systole, left ventricular blood may be forced back into the left atrium and from this chamber into the right atrium. Moreover it is also possible for left ventricular blood to be regurgitated directly through the common atrioventricular valve into the right atrium.

In its fully developed form, the malformation presents a minor defect in the superior part of the posterior portion of the ventricular septum (Figure V-43*b*). This feature may allow direct shunting of left ventricular blood into the right ventricle (Figure V-41).

The main circulatory alteration in cases of persistent interatrial foramen primum is one in which oxygenated blood returning from the lungs is recirculated through the lungs. This places a burden upon the right side of the heart The usual anatomic consequences of this factor are a dilated right atrium, a dilated and hypertrophied right ventricle and an unusually wide pulmonary trunk As in cases of atrial septal defect in the region of the foramen ovale, the pulmonary trunk may be considerably wider than the aorta, a feature which at times has been considered to represent an additional anomaly This is ordinarily not the case The usual difference in the size of the two vessels can readily be explained upon the basis of the difference in the volume of blood which the two arteries carry. This statement should not be construed to mean that persistent interatrial foramen primum with common atrioventricular canal is never associated with other recognized malformations

Indeed, Sir Arthur Keith (1909) expressed the opinion that association of malformations was the rule On the basis of reports and our own experience this categorical opinion cannot be supported. When other malformations are associated, they may take the following forms. situs inversus, pulmonary atresia and corrected transposition (Beattie, 1922); Eisenmenger complex (Goetsch, 1938), the tetralogy of Fallot (Plauchu and Gardère, 1909), bicuspid pulmonary valve (Preisz, 1890, Case 3, and Abbott, 1936), patent ductus arteriosus (Rudolph, quoted by Soldner, 1904); and persistent left superior vena cava (Turner, 1892).

The case reported by Benjamin, Landt and Zeck (1940), concerned a girl 18 years old whose heart showed a narrow pulmonary trunk and hypoplasia of the right ventricle associated with the malformation under discussion Clinically this patient showed extreme degrees of cyanosis and

clubbing of the digits. These two features are contrary to the findings in cases of persistent interatrial foramen primum and common atrioventricular canal in uncomplicated form.

Persistence of the common atrioventricular canal is almost a constant feature in cases of cor biloculare and in some cases of cor triloculare (Cunningham, 1948). In hearts in which there is failure of formation of four cardiac chambers, persistence of the common atrioventricular ostium should be considered an incidental manifestation of a more serious defect. In the interest of accurate classification of congenital cardiac disease, hearts which have two or three chambers and a common atrioventricular canal should be classified on the basis of the more serious defect of which persistent common atrioventricular canal is merely an integral part. These anomalies should be segregated from those in which persistence of the common atrioventricular canal is the major and essential defect.

Persistent interatrial foramen primum with common atrioventricular valve represents about 1 5 to 4 per cent of major anomalies of the heart and great vessels. There were two examples of this malformation in the collection of 105 specimens reviewed by Gibson and Clifton (1938) In the Mayo Clinic collection there are nine examples among 212 specimens of major anomalies of the heart and great vessels.

There is no predilection for either sex. About one-fifth of patients with the condition die before the end of the first month of life More than one-half of the patients die before they reach the end of the first year of life and only a small percentage of the rest reach adult life.

Rogers and Edwards (1948) reviewed 54 cases in which data as to age were available; only five of these 54 patients lived beyond the age of 30 years.

The usual cause of death is cardiac failure and pneumonia. Bacterial endocarditis is an unusual complication. When present, it usually involves the deformed valves rather than the margins of the septal defects. Bacterial endocarditis occurred in Goetsch's patient, a girl aged 18 months; in a man aged 23 years observed by Rudolph; and in a man aged 36 years reported by Rogers and Edwards (Figure V-44).

Clinically it is difficult to distinguish persistent interatrial foramen primum with common atrioventricular canal from the more common forms of atrial septal defect, that is, those occurring in the region of the foramen ovale. This is to be expected, since the functional alterations caused by the two malformations are essentially similar. One difference, in general, is that patients with the ordinary type of atrial septal defect usually do not have symptoms of the defect during infancy or childhood; on the contrary, patients with persistent interatrial foramen primum and incomplete division of the atrioventricular canal often do suffer from the defect during infancy. Moreover there is a frequent, though not constant, association between the latter malformation and mongolian idiocy.

Of 56 cases which Rogers and I reviewed, mongolian idiocy was recorded in 17 cases and was absent or could be assumed to be absent in eight cases; in the remaining 31 cases the presence or absence of mongolian idiocy could not be determined from the histories. Since the time of our review, Wurtz and Powell (1948) have reported a case of this cardiac malformation which was associated with the Eisenmenger complex and mongolian idiocy. Their patient was an infant aged nine months. Albores and Caprile in 1944 reported on the clinical and pathologic features in their patient, a boy aged 55 days, who had mongolian idiocy. Rogers and the author did not review this case.

It should be emphasized that when mon-

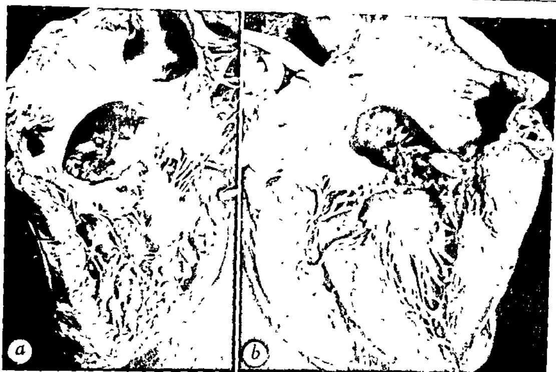


Figure V-44. Subacute bacterial endocarditis complicating patent interatrial foramen primum with partial persistence of the common atrioventricular canal in a man 36 years old

a Viewed from the right, the inferior part of the atrial septum shows a defect immediately above an essentially normally developed tricuspid valve. Vegetations in the left side of the heart are seen through the atrial septal defect The region of the foramen ovale is normally formed There is right ventricular hypertrophy (From Tinney and Barnes *Minnesota Med*, 25 637-643, 1942 Reproduced by permission of the authors and *Minnesota Medicine*)

b The left side of the heart The defect in the inferior part of the atrial septum and the cleft in the mitral valve are similar to the changes in these regions illustrated in Figure V-42*b* In addition vegetations of subacute bacterial endocarditis are deposited on the anomalous valve (From Rogers and Edwards, 1948 Reproduced by permission of the C V Mosby Company)

golian idiocy occurs with congenital cardiac disease the malformation usually is patent interatrial foramen primum with persistent common atrioventricular canal, but it may be associated with any of the known types of cardiac malformation

Clinical evidence of right ventricular enlargement and dilatation of the pulmonary trunk may be encountered in a study of cases of patent interatrial foramen primum. Cyanosis may be present at birth but is usually not persistent. At this early age cyanosis usually appears with exertion, as when the infant cries

In our review, it was found that cyanosis had occurred at some time during the patient's life in 23 of the 56 cases. It was recorded as absent in seven cases and in the remaining 26 cases no mention of this sign was present in the reports reviewed A murmur, usually described as systolic in time, was recorded in 22 of 25 cases in which the history seemed adequate

The number of cases in which electrocardiographic studies had been made is inadequate, though from an anatomic point of view it is expected that this test would give results essentially like those obtained in the more common types of atrial septal defect. Though the results of cardiac catheterization in this condition have not been correlated with pathologic findings, it is anticipated that the usual findings would be those of arterialization of the

right atrial blood combined with unusual peaks in right atrial pressures. The latter is expected to result from the effects of ready communication between the left ventricle and the right atrium.

The developmental basis for the malformation known as persistent interatrial foramen primum with common atrioventricular canal is explained as follows: The dorsal and ventral atrioventricular endocardial cushions are deficient in growth and fail to fuse; the mitral and tricuspid orifices do not form Instead, the embryonic atrioventricular canal remains common to both sides of the heart, as in the young embryo. (See Figure II-17, and compare with Figure V-41.) The so-called cleft condition of the anterior or aortic leaflet of the mitral valve and of the septal leaflet of the tricuspid valve is a manifestation of this failure of the two atrioventricular endocardial cushions to fuse. Normally each of the two leaflets named is a conjoined leaflet, being composed of tissue from the dorsal and from the ventral atrioventricular endocardial cushions. The large anterior leaflet of the common atrioventricular valve represents the evolution of the ventral atrioventricular endocardial cushion, which has failed to fuse with the dorsal one. Likewise, the posterior leaflet of the common atrioventricular valve represents differentiation of the dorsal atrioventricular endocardial cushion.

The defect of the inferior portion of the atrial septum follows as a result of failure of interatrial septum primum to fuse with the atrioventricular endocardial cushions. The defect represents essentially the picture of the embryo illustrated in Figure II-16*b*. Failure of the fusion of interatrial septum primum with the endocardial cushions is probably the responsibility of the cushions. Normally these have a certain height and so are able to make contact and to fuse with the septum primum, which grows toward them. Evidently, when the cushions are deficient, they are deficient not only in a dorsoventral direction but also cephalocaudally.

A similar explanation probably applies to the ventricular septal defect that may be present in some cases of the malformation. While the ventricular septum plays no role in the partitioning of the atrioventricular canal, the superior portion of the posterior part of the developing ventricular septum fuses with the atrioventricular endocardial cushions. When the cushions are deficient in size they may fail to fuse with the ventricular septum. Not being tacked to the cardiac skeleton in the region of the atrioventricular canal, the growing ventricular septum develops a defect in its superior region.

As stated, in certain cases of persistent interatrial foramen primum with common atrioventricular canal the inferior limbus of the fossa ovalis is defective (Figure V-40*b*). This seems to be explained as a result of failure of the septum primum to join with the atrioventricular endocardial cushions. Septum secundum, from which the limbus of the fossa ovalis develops, seems to depend for full growth on the splinting action of a fully formed septum primum.

Tricuspid Atresia

On the basis of a review of the literature and of their own material, Edwards and Burchell (1949) presented an anatomic classification of tricuspid atresia. This was essentially an elaboration of a classification proposed in 1906 by Kuhne. In all cases of tricuspid atresia the heart functions as a two-chambered heart. These hearts have certain anatomic features in common, although some differences may exist from case to case. The classification depends upon the differences between specimens. Common to all the cases are (1) atresia of the tricuspid orifice; (2) patency of the atrial septum; and (3) a large

mitral orifice leading into a large ventricular chamber. It seems pertinent to consider the foregoing features in somewhat greater detail.

No tricuspid orifice is present and usually no tissue is recognizable as that of the tricuspid valve. There may be a depression or some localized fibrous thickening of the floor of the right atrium at the expected location of the tricuspid orifice.

Patency of the atrial septum is, in the majority of cases, represented by a retention of the fetal type of foramen ovale There is an adequate channel leading from the right atrium into the left. In the cases reviewed there were none that had small and inadequate atrial septal channels. As in the normal fetus, there is usually a fully developed valve of the foramen ovale but this is held away from the atrial septum by the column of blood which flows from the right atrium into the left. In cases of tricuspid atresia this channel is usually the only outlet for blood entering the right atrium through the venae cavae and the coronary sinus. Less commonly the inferior part of the atrial septum is described as defective, and the region of the foramen ovale shows a normal postnatal condition. At times the atrial septum is represented only by a rudimentary membrane which, because of its small size, is ineffective in partitioning the two atrial cavities There is then, in effect, a single atrium It is to be emphasized, however, that defects of the atrial septum other than patency of the foramen ovale are the exception rather than the rule in the reported instances of tricuspid atresia.

It is common for the right atrial chamber to be wider than normal and its wall thicker. Since all the incoming blood, both peripheral and pulmonary, ultimately collects in the left atrium, the latter chamber is usually wider than normal. Similarly, since all of the incoming blood must pass through the mitral orifice to enter the ventricular part of the heart, the mitral orifice is wider than one would find in a normal heart of a person of comparable age. Though its orifice is wider than normal, the mitral valve is normally formed and its leaflets are sufficiently developed to guard the left atrioventricular orifice adequately. In all cases of tricuspid atresia the mitral orifice leads into a large ventricular chamber from which all the blood circulating through the heart must pass on its way to the great arterial trunks.

The relation of the great vessels to each other and to the ventricular part of the heart varies in cases of tricuspid atresia The varieties of interarterial relationships and arterioventricular relationships constitute four groups, which form the basis for the anatomic classification of congenital tricuspid atresia presented in Table V-4.

TABLE V-4

Congenital Tricuspid Atresia, Anatomic Classification

Type I No transposition of the great vessels
- a. Pulmonary atresia. Closed ventricular septum
- b Subpulmonary stenosis

Type II. Transposition of the great vessels
- a Pulmonary or subpulmonary stenosis
- b No pulmonary or subpulmonary stenosis

Type Ia. No Transposition of the Great Vessels. Pulmonary Atresia. Closed Ventricular Septum

(See Taussig, 1936, 1947, Figure V-45a) *In this type of tricuspid atresia the left ventricle has a large capacity and its wall is thick.* The ventricular septum is completely formed. The two ventricles are greatly disproportionate in size. The right ventricle is minute and lies virtually hidden in the superior portion of the right wall of the large left ventricle, its small size is explained by its failure to play any role in the circulation It is merely an isolated endocardium-lined chamber, since both the tricuspid and the pulmonary valve orifices are atretic. Its very thin wall contrasts with the condition of the right ventricle

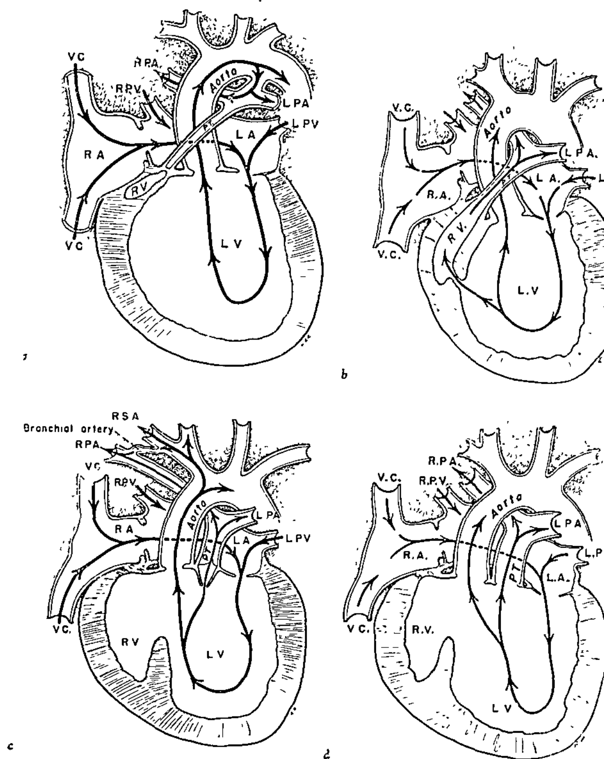


Figure V-15 The four anatomic types of tricuspid atresia.

a. Type Ia Pulmonary atresia Closed ventricular septum. No transposition of great vessels.

b. Type Ib Subpulmonary stenosis No transposition of great vessels.

c. Type IIa. Subpulmonary stenosis Transposition of the great vessels

d Type IIb No pulmonary or subpulmonary stenosis. Transposition of the great vessels

in cases of isolated pulmonary atresia (see Isolated Pulmonary Atresia) Though the intracardiac circulation is virtually identical in these two conditions, hearts in which the tricuspid orifice is patent show tremendous hypertrophy of the right ventricular wall. The right ventricular chamber, however, remains small In tricuspid atresia, Type Ia, both the right ventricular chamber and wall are so small that the presence of the right ventricle may easily be overlooked It is possible that certain cases reported as instances of single ventricle may, in effect, be examples of this malformation When the right ventricle is believed to be present, it may require preparation of microscopic sections taken from the expected location of the right ventricle to prove conclusively that this chamber in fact exists The pulmonary atresia usually occurs at valve level, the pulmonary trunk superior to valve level being hypoplastic but patent The aorta and the pulmonary trunk are correctly interrelated, no transposition being present The ductus arteriosus is usually patent and constitutes the major channel by which the lungs receive blood.

Type Ib. No Transposition of the Great Vessels. Subpulmonary Stenosis

(See Figure V-45*b* Consult reports by Aschoff and Schreiber, 1901, Bellet and Stewart, 1933, Breslich, 1930, Brown, 1936, Cohn, 1904, Crocker, 1879, Edwards, Dry and Logan, 1948, Geisler, 1930, Grayzel and Tennant, 1934, Hammond, 1937, Holder and Pick, 1939, Huebschmann, 1921, Kuhne, 1906, Miale, Millard, Beno and Custer, 1948, Monckeberg, 1924; Nuhn, 1865, Rihl, Terplan and Weiss, 1929, Schuberg, 1861, Sieveking, 1854; Wieland, 1914) This is the most common type of tricuspid atresia The great vessels are correctly interrelated. The aorta is of normal caliber or wider than normal. The pulmonary trunk is somewhat narrower than normal but usually is of adequate caliber to carry a sufficient amount of blood to the lungs, were there no subpulmonary stenosis In almost one-half of the cases the pulmonary valve is bicuspid. Usually this does not cause any pulmonary stenosis, but at times the configuration of the bicuspid valve is such as to be responsible for pulmonary stenosis (Crocker, 1879).

Examination of the ventricular part of the heart reveals a large ventricular chamber into which blood flows through the mitral orifice. The large ventricular chamber communicates freely with the aorta (Figure V-46*a*) In addition the large chamber communicates by means of a narrow tract, often described as being entirely muscular-walled, with a smaller narrow ventricular chamber (Figure V-46*b*). The latter lies obliquely along the right superior aspect of the ventricular mass In an occasional case two openings are present between the two chambers, as in the cases of Bellet and Stewart and of Grayzel and Tennant The superior extremity of the small ventricular chamber communicates with the pulmonary orifice. The tract connecting the two ventricular chambers is usually narrow and constitutes the major barrier to the flow of blood from the larger ventricular chamber to the lungs. In addition, the diminutive size of the smaller ventricular chamber may constitute another cause of subpulmonary stenosis in this type of tricuspid atresia

At the time of death the ductus arteriosus is usually closed or admits only a fine probe

In an occasional case it is found open, as in the case of Holder and Pick, in which the patient was 10 months old at the time of death. In the case of Rihl, Terplan and Weiss there was no vestige of a ductus arteriosus. In Case 2 of Huebschmann the ductus arteriosus ran between the right pulmonary artery and the innominate ar-

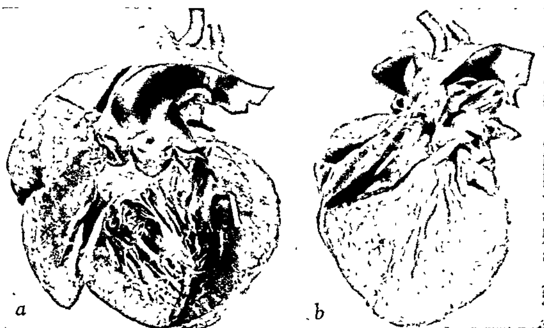


Figure V-46. Tricuspid atresia Type Ib in a female infant three and one-half months old.
a The aorta is in free communication with the left ventricle The probe lies in a narrow muscular tract leading from the left ventricle upward into a hypoplastic right ventricular chamber (see *b*) (From Edwards, J. E., *Postgrad Med*, *3* 327-341, 1948 Reproduced by permission of Postgraduate Medicine.)
b The upper end of the probe shown in *a* lies in the hypoplastic right-sided ventricular chamber The pulmonary orifice is in communication with the cephalic end of this chamber The pulmonary valve is bicuspid. There is no transposition of the great vessels. (From Edwards, J E, Dry, T. J, and Logan, G. B: *Bull Internat A M Museums, 28* 34-42, 1948 Reproduced by permission of the *Bulletin of the International Association of Medical Museums*)

tery, there were no other anomalies of the aortic arch system in this case. Nor were there any major malformations of the aortic arch system in the remaining cases reviewed by us, excepting that of Grayzel and Tennant. No instances of right aortic arch and right descending aorta, such as occur in from 20 to 25 per cent of the cases of the tetralogy of Fallot, were described in cases of tricuspid atresia of any type.

Type IIa. Transposition of the Great Vessels. Pulmonary or Subpulmonary Stenosis

(See Blackford and Hoppe, 1931; Corsdress, 1924; Hedinger, 1915; Kroop, 1951, Lev and Saphir, 1937; Manhoff and Howe, 1945; Rogers, Cordes and Edwards, 1950; Smetana, 1929, Sommers and Johnson, 1951.) (Figure V-45*c*.) As in all types of tricuspid atresia, this type displays a large mitral orifice which leads into a large ventricular chamber. Transposition of the great vessels is present (Figure V-47) There is, as well, a small or diminutive ventricular chamber which lies along the right side of the larger chamber and appears as a diverticulum thereof (Figure V-47*b*). Between the two ventricular cavities are two muscular ridges. One lies along the posterior wall of the ventricular part of the heart. Superiorly, it lies just to the right of the transposed pulmonary orifice in the main ventricular chamber. It extends downward in an oblique direction, usually to the right, to end in the posterior wall of the smaller chamber. This ridge is the crista supraventricularis. By its presence it tends to divide the ventricular part of the heart into two chambers. The second muscular ridge lies in a vertical position





Figure V-47 Tricuspid atresia Type IIa in a boy 12 years old (From Edwards and Burchell, 1949 Reproduced by permission of the W. B Saunders Company)

a The unopened heart and the opened aorta The aorta arises in an anterior transposed position The pulmonary trunk lies behind the aorta and is hidden in a shadow. The ligamentum arteriosum extends from the left pulmonary artery to the aorta.

b The left ventricular chamber has been opened The lower large probe lies in the mitral orifice. The upper large probe lies in the diminutive right-sided ventricular chamber The small probe lies in the stenotic subpulmonary orifice, which is bordered by the crista supraventricularis (*C S*) on the right and the anterior leaflet of the mitral valve (*M.*) on the left. The transposed aorta is in free communication with both ventricular chambers In spite of the appearance of two ventricular chambers, the free communication between the two cavities produces, in effect, a single ventricle.

extending cephalically from the right wall of the ventricular mass This muscular ridge perhaps represents the muscular part of the ventricular septum. The division of the ventricular part of the heart into a large and a small chamber is *accomplished largely* by *this* ridge. Its superior margin *is* free and through its overlying space the two chambers communicate

The pulmonary trunk arises dorsal to and usually to the left of the aorta (Figures V-47*b* and V-48) The two vessels *ascend vertically* parallel to one another. The pulmonary trunk arises from the large ventricular chamber and its ostium is closely approximated to the anterior leaflet



Figure V-48 Tricuspid atresia, Type IIa (Other illustrations of this case appear in Figures V-47 *and* V-49) *Close-up view of the* outflow region

the crista *supraventricularis* (*C S*) on the right and *the anterior* leaflet of the mitral valve (*M*) on the left. (From Edwards and Burchell, 1949 *Reproduced by* permission of the W. B Saunders Company.)

of the mitral valve, which lies to the left of the subpulmonary region. The aorta is of normal caliber and arises either completely from the diverticulum-like chamber or from both ventricles superior to the site of their communication.

The pulmonary trunk is often of normal caliber but this may be somewhat reduced. In the specimen of this type of tricuspid atresia which Rogers, Cordes and Edwards (1950) observed, the trunk was narrower than normal but not stenotic While stenosis may exist at valve level or in the pulmonary trunk, as in the cases of Manhoff and Howe and of Lev and Saphir, it usually is subpulmonic Immediately inferior to the pulmonary orifice the anterior leaflet of the mitral valve, lying to the left, is close to the superior extremity of the crista supraventricularis. Between these two structures is the subpulmonary tract. A bridge of fibrous tissue, which sometimes contains foci of calcium and which extends between the anterior leaflet of the mitral valve and the crista supraventricularis, encircles and narrows the subpulmonary tract (Figures V-48 and V-49). Since blood on its way to the pulmonary trunk must pass through this tract, a barrier exists to flow in the subpulmonary region The ductus arteriosus usually closes normally.

In the case reported by Rogers, Cordes and Edwards, in which the patient was a boy aged 12 years with tricuspid atresia, Type IIa, the bronchial arteries were dilated and had probably served to carry a substantial amount of blood to the lungs.



Figure V-49 Tricuspid atresia, Type IIa. (Other illustrations of this case appear in Figures V-47 and V-48) The stenotic subpulmonary tract has been opened The tract is bounded on the right by the *crista supraventricularis (C S.) and on the left by* the anterior leaflet of the mitral valve (*M*) *P V* one leaflet of a bicuspid pulmonary valve. *P T*

wards and Burchell, 1949. Reproduced by permission of the W B Saunders Company)

Type IIb. Transposition of the Great Vessels. No Pulmonary or Subpulmonary Stenosis

(See Dickson and Jones, 1948, Dunsky, 1947, Kroop, 1951, Robertson, 1911, Robinson and Howard, 1948; Wason, 1934.) (Figure V-45*d*.) The malformation of this type is identical with Type IIa in all respects except for the state of the pulmonary circulation. In Type IIb the pulmonary trunk arises posterior to the aorta as in Type IIa but there is no pulmonary or subpulmonary stenosis.

In contrast to the situation in tricuspid atresia of Type IIa, there is in Type IIb no barrier to pulmonary blood flow. It is conceivable that the failure of patients with Type IIb tricuspid atresia to survive beyond infancy may be explained on the basis of excessive pulmonary blood flow at the expense of peripheral blood flow.

Tricuspid atresia, Type Ib, is by far the most common type of the malformation. Of 45 cases of tricuspid atresia of all types studied, 42 of which had been reported by others, Edwards and Burchell found four cases of Type Ia, 28 of Type Ib, eight of

Type IIa and five of Type IIb Tricuspid atresia of any type is a relatively uncommon form of cardiovascular malformation

Abbott (1936) listed its occurrence 16 times among 1000 cases of cardiovascular malformations, and Gibson and Clifton (1938) had one example of tricuspid atresia among 105 specimens of congenital anomalies of the heart and great vessels. In the Mayo Clinic collection of 212 specimens of major anomalies of the heart and great vessels there are four examples of tricuspid atresia

Developmental Basis. Little of authoritative nature can be said concerning the developmental basis for tricuspid atresia It can be stated that in Type Ia the atresia probably occurs at a relatively late period in cardiac development, since the ventricular septum is properly formed This would indicate that the atresia had occurred some time after the eighth week of intra-uterine life It is inconceivable that the alterations in circulation which the atresia would produce would allow a ventricular septum not yet formed to go on to normal development The concept that Type Ia atresia develops late is further supported by the fact that tissue suggestive of valvular tissue has been identified at the site of the atretic valve (Taussig, 1936)

The other three forms of tricuspid atresia, Types Ib, IIa and IIb, probably develop before the ventricular septum is formed, since a study of the ventricles in these cases reveals features which might be interpreted either as patency of the ventricular septum or as a complete lack of formation of ventricular septum It would seem appropriate to state that in these three latter types the atresia occurs before the ventricular septum would be expected to be complete, that is, before the eighth week of embryonic life While it is possible that the basis for tricuspid atresia is set before the atrioventricular canal is partitioned, it is reasonable that the atresia *occurs after the previously*-common atrioventricular canal has been partitioned into tricuspid and mitral orifices. If this is so, tricuspid atresia of the types under discussion occurs between about the fourth and the eighth weeks of embryonic life

Similar attempts have been made to explain the basis for tricuspid atresia as for mitral atresia.

Three different phenomena have been cited. (1) abnormality of the atrial septum, (2) abnormality of the ventricular septum, and (3) fetal endocarditis.

The view of Monckeberg was that tricuspid atresia is caused by maldirection of growth of the atrial septum This hypothesis has been logically taken to task by Scriba (1937), who pointed out that in most of the cases of tricuspid atresia, an abnormal direction of growth on the part the atrial septum is either absent or not proved Scriba further emphasized that there are examples of misplacement of the atrial septum without atresia of either of the atrioventricular ostia A further argument against the views of Monckeberg on this matter is that in certain cases of tricuspid atresia the atrial septum is incompletely formed, its lower margin hanging unattached. It seems reasonable to assume that at least in some of the cases, Monckeberg's explanation is not tenable

Those cases of atresia of the tricuspid orifice in which two ventricles are present constantly show a large left ventricle and a small right ventricle. In this way, the ventricular septum is eccentric with respect to the ventricular portion of the heart taken as a whole. The superior portion of this septum is often in close proximity to the expected position of the tricuspid orifice and so it might be argued that the eccentric ventricular septum is responsible for the closure of the tricuspid orifice It should be emphasized that the

conditions within the ventricular portion of the heart may logically be viewed as the result of the abnormal circulatory conditions set into motion by the tricuspid atresia, rather than as causing that anomaly. Further evidence against the view that tricuspid atresia is caused by an eccentric ventricular septum is supplied by those cases of isolated pulmonary atresia. In this group of cases, the left ventricle is large, the right ventricle is small and the ventricular septum is eccentric Nevertheless, tricuspid atresia need not be associated.

Farber and Hubbard (1933) have supplied evidence which supports the thesis that certain instances of valvular stenosis and atresia are the result of fetal endocarditis. In the opinion of these authors, anomalies which result from such inflammation occur in rather late stages of cardiac development. On this basis it is conceivable that tricuspid atresia Type Ia might result from an inflammatory process but such an explanation would seem inappropriate as an explanation for the other types of this malformation.

Significant Clinical and Laboratory Features. The patient with tricuspid atresia is usually cyanotic, although that is not always true. The electrocardiogram is of considerable help in most of the cases and classically shows left axis deviation. This finding, however, is not always present for in some cases no axis deviation may be identified (Gasul *et al.*, 1950; Kroop and Grishman, 1950, Sommers and Johnson, 1951). In one case there was complete heart block (Dickson and Jones, 1948) The roentgen examination of the thorax may be helpful. In the anteroposterior view there is a concavity in the region of the pulmonary trunk which resembles that in the tetralogy of Fallot. The left anterior oblique view reveals evidence consistent with underdevelopment of the right ventricle. Clubbing of the fingers and toes develops in patients who survive infancy and polycythemia is usually present.

The age at death is usually low. Patients with Type Ia rarely, if ever, survive infancy. Of the 28 cases of Type Ib which were reviewed the longest survival was four years and the shortest was 10 hours. The mean age at death in Type Ib is slightly more than seven months.

The cases of Type IIa represent the group with the longest survival. Into this group falls the often-quoted case of Hedinger (1915), of a woman who died at the age of 56 years after leading an active life The patient of Rogers, Cordes and Edwards died at the age of 12 years. Patients with tricuspid atresia of Type IIb die at an early age, usually in early infancy.

It is evident from the varied anatomic pictures seen in cases of tricuspid atresia that the functional disturbances caused by the malformation in a given case may vary considerably from those in another case. In Types Ia, Ib and IIa, pulmonary stenosis is a prominent feature. In each of these types the malformation may be compared functionally to the tetralogy of Fallot, since, as in the tetralogy of Fallot, the ventricular ejectile force responsible for sending blood to the lungs also sends blood to the systemic circulation, and pulmonary stenosis is present. For these types anastomosis of a systemic to a pulmonary artery is advantageous (Potts and Gibson, 1948). In tricuspid atresia, Type IIb, on the contrary, there is no pulmonary stenosis present. As in the other types of tricuspid atresia, the same ventricular force supplies blood to both the pulmonary and systemic circulations. In this connection, tricuspid atresia, Type IIb, functions not like the other types of tricuspid atresia or like the tetralogy of Fallot, but like the heart in the Eisenmenger complex. From the foregoing it is apparent that from a functional point of view there is a great variation among cases of tricuspid atresia

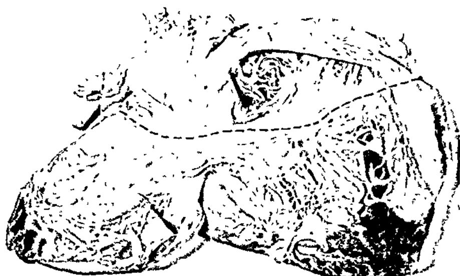


Figure V-50 Ebstein's malformation of the tricuspid valve Case of Dr Donald deF Bauer (1945) (Reproduced by permission of Dr Bauer and *American Journal of Roentgenology and Radium Therapy*) The interior of the right side of the heart is shown Part of the attachment of the tricuspid valve is at a lower level than the annulus fibrosus The attachments of the tricuspid valve leaflets are outlined in the white dotted line The black dotted line indicates the location of the annulus fibrosus, the normal line of attachment for the tricuspid valve

so that different types of tricuspid atresia may bear less resemblance to each other than to malformations which have quite different anatomic configurations

Ebstein's Malformation of the Tricuspid Valve

Ebstein's (1866) malformation of the tricuspid valve is characterized by deformity of the attachment of the valve leaflets While part of the anterior tricuspid valvular tissue is normally attached to the annulus fibrosus of the valve, the remainder of the leaflets arise from the right ventricular wall and the ventricular septum. Thus, part of the tricuspid valve is displaced inferiorly and part of the right ventricular cavity is anatomically continuous with the right atrial cavity That part of the right ventricle which functions as such is small (Figure V-50). The foramen ovale is often patent. According to Walton and Spencer (1948), the foramen ovale was patent in 16 of the 19 reported cases

Patients with this malformation usually survive to adult life, the average age at death in the cases reviewed by Walton and Spencer being 25 years. Three of these patients were reported to have had normal health for more than 50 years (Marxsen, also Malan, quoted by Yater and Shapiro, 1937, Walton and Spencer, 1948).

Among the complications of Ebstein's malformation, sudden death is reported four times (Bauer, 1945); paradoxic embolism was reported by Geipel (1903) and by Walton and Spencer, while Heigel's (1913) patient, a girl of 10 years, died with cerebral abscess but without bacterial endocarditis In the review of Yater and Shapiro, on Ebstein's malformation, it is stated that few clinical signs are usually associated with tricuspid insufficiency, owing to the presence of a large right atrium which acts as a buffer in receiving regurgitated blood, and of patency of the foramen ovale. Through the latter, blo

may escape into the left atrium and so avoid back pressure upon the large veins. The usual signs of tricuspid insufficiency are seen when cardiac failure appears. Cyanosis is not constant but, when present, is explained by Yater and Shapiro as being caused by reverse blood flow through the foramen ovale into the left side of the heart, thus diminishing pulmonary blood flow and producing a venous-arterial shunt. The rarity of Ebstein's malformation is indicated by the fact that Yater and Shapiro were able to collect only 15 cases from the literature up to 1937. They added one case Walton and Spencer (1948) reported one case and referred to two others reported by Zink (1937) and Bauer (1945) More recent reviews are those of Baker and associates (1950) who added two cases, and of Engle and associates (1950) who added three cases. The latter authors believed that the tricuspid valve was competent. Barger and co-workers (1951) reported a case in which absence of the pons was a fatal complication. Reynolds (1950) reported a case diagnosed clinically

Two specimens of this cardiac malformation are among the 212 cases of major cardiovascular malformations in the pathologic collection of the Mayo Clinic.

Mitral Atresia

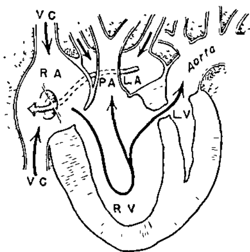
Congenital mitral atresia is a rare malformation usually causing death of the patient during early infancy (Brockman, 1950, Large, 1950). Mitral atresia may be associated with atresia of the aortic orifice or it may be the only basic malformation in a given case The association of mitral atresia and aortic atresia will be discussed in another section (see page 401).

In cases of mitral atresia the mitral orifice usually is represented by a blind depression when viewed from the left atrial



Figure V-51 Mitral atresia in a male infant four months of age The left atrium has been opened Near the base of the auricular appendage there is a blind depression marking the expected location of the mitral orifice In the atrial septum, several wide thebesian veins are present anterior to a small transatrial communication The latter is a patent foramen ovale The lining of the left atrial endocardium is gray and thick A diagrammatic representation of the intracardiac circulation in this case appears in Figure V-52*a* (From Dry and associates, *Postgrad Med*, 4 231-263, 1948 Reproduced by permission of the authors and *Postgraduate Medicine*)

aspect (Figure V-51). No elements of the mitral valve are identifiable. The left atrium often is smaller than normal, as in Wenner's case (1909). The chief outlet for blood coming into the left atrium from the pulmonary veins is a patent foramen ovale (Figures V-51 and V-52*a*). At times, the thebesian veins in the atrial septum are wider than normal and may carry some blood from the left atrium into the right. This route, however, must be of minor importance. The appearance of the patent foramen ovale is usually quite characteristic. The valve of the foramen ovale seems to be normally formed so that, in normal circumstances, it would prevent left atrial blood from flowing into the right atrium.



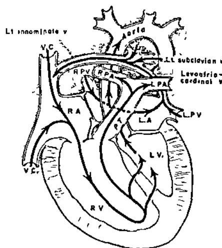


Figure V-52 *a* Intracardiac circulation in a case of mitral atresia in a male infant four months old (see Figure V-51) A patent foramen ovale is the outlet for the left atrium There is a ventricular septal defect The transposed aorta arises from a small left-sided ventricular chamber (From Edwards, J E *Postgrad Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

b Mitral atresia in a female infant 21 days old In contrast to the usual situation in this malformation as shown in *a*, the foramen ovale is closed There is an anomalous vein (levoatriocardinal vein) running between the left atrium and the left innominate vein In this way, left atrial blood flows towards the right atrium There is no transposition of the great vessels The two ventricles communicate by means of defects in the muscular part of the ventricular septum (see Figure V-11) (From Edwards and DuShane, 1950 Reproduced by permission of *Archives of Pathology*)

Probably as a consequence of the great pressure which is built up within the left atrium, the valve of the foramen ovale is forced through the foramen ovale into the right atrium, thus creating a peculiar type of patency.

In the case of McIntosh (1926) the foramen ovale was prematurely closed, thus preventing the flow of blood across the atrial septum. An anomalous vein ran between the left atrium and the superior vena cava, thereby allowing an indirect communication between the left atrium and the right A second case of this type was encountered by Edwards and DuShane (1950). In that case, the anomalous vein ran between the left atrium and the left innominate vein (Figure V-52*b*) The developmental basis for this type of vein (levoatriocardinal vein) will be discussed in another section (see page 496).

In all cases of mitral atresia the blood returning to the heart from the lungs ultimately reaches the right atrium. At the same time, the right atrial chamber receives, in a normal manner, blood from the venae cavae and the coronary sinus, thus the right atrial chamber is usually greatly dilated and its wall is hypertrophied. The tricuspid orifice represents the only communication between the atrial part of the heart and the ventricles

The structure of the ventricular part of the heart varies in cases of mitral atresia. Probably the most common form is that with but one ventricle (Bergman and Morales, 1948, Scriba, 1937, McIntosh, 1926, Walls, 1941). In other cases, there is a ventricular septal defect in the region of the membranous portion of the septum. In still others, the membranous portion of the ventricular septum is intact, but there

are perforations in the muscular portion of the septum

The course and relations of the great arteries leading from the heart vary. In most cases in which there is a common ventricle, the great vessels are transposed

The case of Bergman and Morales, of mitral atresia in an infant girl five and one-half months old, is an exception in that, in the presence of a common ventricle, there was no transposition of the great vessels. In the Mayo Clinic collection of 212 specimens with major cardiovascular malformations there are five examples of mitral atresia In one case, that described by Edwards and Rogers (1947), in which the subject was an infant boy four months old, the foramen ovale was patent, and there was a defect in the membranous part of the ventricular septum (Figure V-52*a*). The great vessels were transposed, the aorta lying ventral to and to the left of the pulmonary trunk The aorta arose from a diminutive ventricle while the pulmonary trunk arose from the right ventricle In a second case the subject was an infant boy three months old. In this case there was likewise a patent foramen ovale. There was a common ventricle associated with transposition of the great vessels, the aorta arising in front and to the right of the pulmonary trunk (Figures V-53*a* and V-53*b*). In a third case, that reported by Edwards and DuShane (1950), the subject was an infant girl 21 days old In this case, the foramen ovale was prematurely closed. The membranous portion of the ventricular septum was intact, but there were perforations of the muscular portion (Figure V-11) No transposition of the great vessels was present. The left atrium communicated with the left innominate vein by means of an anomalous vessel (Figure V-52*b*).

The occurrence of five cases of mitral atresia among 212 cases of various major cardiovascular malformations is an unusually high incidence of mitral atresia. Abbott (1936) included but five cases of this malformation among 1000 cases of congenital cardiac disease. In 1945 Manhoff and Howe stated that 28 cases of mitral atresia had been reported prior to

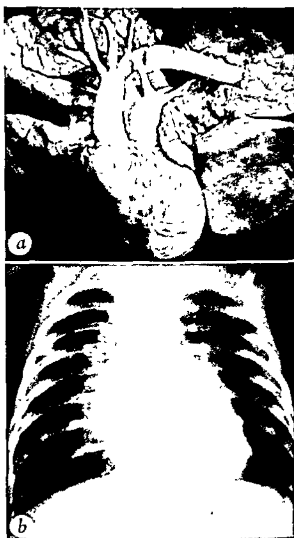


Figure V-53 Mitral atresia with transposition of the great vessels in a male infant three months old.

a Ventral view of exterior of the heart, great vessels and portions of the lungs. The ligamentum arteriosum extends in a normal way from the left pulmonary artery to the aorta There is transposition *of the great vessels, the aorta arising ventral to* and slightly to the right of the pulmonary trunk The left auricular appendage lies beside the pulmonary trunk In this case, there was a common ventricle The descending aorta has been deflected in front of the left lung.

b Roentgenogram of the thorax in the case of mitral atresia illustrated in *a* The right atrial shadow is wide. The prominent shadow at the left side of the base of the heart is probably caused by the left atrium

the time of their paper They described an additional case.

The functional effects of mitral atresia are to create in essence a two-chambered heart. Since the pulmonary trunk is usually of normal width, it might be expected that the adequate arterial channel to the lungs would prevent cyanosis Cyanosis may, however, be present, and may be explained on the basis of pulmonary stenosis in the form of impaired venous return from the lungs It has been shown that the route of exit for blood in the left atrium is dependent upon either a small opening in the foramen ovale or an anomalous vein leaving the left atrium In the usual case, neither of these routes alone is adequate to allow unimpaired venous flow from the lungs. It seems reasonable to assume that in these cases there is an elevated pulmonary vascular pressure, on the basis of impaired venous return. This phenomenon would, if it reached sufficient proportions, tend to make blood in the ventricles flow more readily into the aorta than into the pulmonary trunk Under these circumstances, while no arterial stenosis existed, there would, in effect, be the venous-arterial shunt similar to that seen in cases of stenosis of the major arterial pathways to the lungs The usual case of mitral atresia, therefore, represents a functional two-chambered heart in which there is impaired flow of blood to the lungs. It seems reasonable that enlargement of the opening in the atrial septum, or the creation of an opening in the atrial septum if none exists, would tend to relieve the barrier to venous flow from the lungs, and so remove the basis for cyanosis in these cases.

The developmental basis for mitral atresia is poorly understood In the section on tricuspid atresia, hypotheses have been proposed concerning the origin of tricuspid atresia. These are applicable to mitral atresia as well.

Mitral Stenosis. Tricuspid Stenosis

Congenital mitral stenosis and tricuspid stenosis are rare. Either one leads to early cardiac failure which possibly begins during fetal life.

Donnally in 1924 reviewed the subject of *congenital mitral stenosis.* His review of 12 cases included one which he had observed His patient was an infant who died suddenly 57 hours after birth from an attack of cyanosis In this case the mitral leaflets were not differentiated. Instead, the valvular tissue was composed of a funnel-shaped structure projecting into the left ventricle. The opening at the apex of the funnel was but 3 mm. in diameter and represented the mitral orifice. The foramen ovale was open and the left ventricle was a diminutive chamber The aorta was hypoplastic and the ductus arteriosus was patent In this case, it may be assumed that only part of the left atrial blood passed through the stenotic mitral orifice The remainder flowed across the opening in the atrial septum into the right atrium In this way the effects of the mitral stenosis were like those of mitral atresia.

The gross appearance of the heart in the cases which Donnally reviewed was not uniform Of the nine cases in which the state of the atrial septum was mentioned, the septum was closed in six instances and the foramen ovale was patent in three. The ductus arteriosus was patent in six of the seven cases in which this structure was described The aorta was described in seven cases. In five cases it was hypoplastic, while in two instances it was said to be of normal caliber. As a rule the duration of life is short in patients with congenital mitral stenosis.

Among the 12 cases which Donnally reviewed, in eight the duration of postnatal life was two months or less, and only one or two days in five of these instances. Two

patients lived to three years and three and one-half years, respectively.

In 1949 Swan and associates reported the occurrence in a patient aged 18 years of congenital mitral stenosis, a patent ductus arteriosus entered the aorta distal to the location of the aortic coarctation, and occlusive vascular changes were present in the smaller pulmonary arteries. The latter were characterized by hypertrophy and elastification of the media and severe intimal thickening with fibrous tissue. The tissue of the mitral valve was not differentiated into recognizable leaflets Instead, the valvular tissue was represented by a fibrous, cone-shaped structure which projected into the left ventricle. Fifteen perforations, the largest measuring 5 mm. in diameter, provided the only communication between the left atrium and the left ventricle

The developmental basis for congenital mitral stenosis is not a settled matter. Donnally expressed the opinion that in some of the hearts there has been improper molding of the developing valvular tissue. In other instances the structure of the stenotic valve suggests an inflammatory process during fetal life In this connection it seems hardly necessary to mention that in a patient who is shown to have mitral stenosis some months after birth, the question of postnatal inflammatory stenosis must be given careful consideration in an evaluation of the case.

A case in point is that of Newns (1938) whose patient, an infant boy 21 months old, died of congestive cardiac failure. The necropsy revealed a severe degree of mitral stenosis caused by thickening and interadhesion of the valve leaflets. The aortic valve was bicuspid. Since no description of the microscopic appearance of the heart was given, it is difficult to include this case without reservation as an example of congenital mitral stenosis.

Kockel (1909) reported the occurrence in a male newborn of mitral and aortic stenosis and marked fibrous thickening of the left ventricular mural endocardium. The foramen ovale was small but patent. There was extreme dilatation of the right atrium and ventricle. The significance of the right-sided enlargement as related to the mitral stenosis is difficult to evaluate. It seems that the mural endocardial thickening of the left ventricle may have played a large role in causing the secondary changes in the right side of the heart (see *Constrictive Endocardial Sclerosis, page 422*).

Field (1938) reviewed the cases of congenital mitral stenosis on which necropsy had been performed at the Hospital for Sick Children, Great Ormond Street, London, from 1860 to 1938. There were seven cases considered to be examples of congenital mitral stenosis In only one case was the stenotic mitral valve the essential defect. This was the case of Newns, to which reference has already been made. In the remaining six cases there were other abnormalities associated with the mitral stenosis. Two of the cases were described as showing aplasia of the whole of the left side of the heart, one as showing underdevelopment of the left ventricle with a patent ductus arteriosus; one with a large ventricular septal defect and two with tricuspid stenosis. Field stated that the average age at death in the seven cases which she reviewed was six months In 86 per cent of the cases the subjects were male.

Congenital Tricuspid Stenosis is very rare, being less common than tricuspid atresia (Herxheimer, 1910). Peacock (1853) described an instance in a female infant, aged two months, who had had dyspnea and cyanosis. The tricuspid valve showed a diaphragm-like fusion of the leaflets which was considered congenital rather than acquired. There were also two defects in the ventricular septum. In 1945 Lewis described a case of congenital tricus-



...erior leaflet of the tricuspid ... tendineae extend ... Papillary ... From a man 60 years old

pid stenosis in a female infant aged three days The tricuspid leaflets showed focal thickenings, which on microscopic examination were composed of collections of cellular connective tissue In Lewis' case the mitral valve, which was grossly normal, showed essentially the same microscopic picture as the stenotic tricuspid valve This author concluded that the tricuspid stenosis was present on a developmental rather than an inflammatory basis.

Double Orifice of the Mitral Valve or of the Tricuspid Valve

An interesting abnormality of either the mitral or the tricuspid valve is occasionally observed in which the valve has a double orifice When the heart is viewed in the conventional manner the opening is usually seen either in the septal leaflet of the tricuspid or in the anterior leaflet of the mitral valve Attached to the margins of the defect are chordae tendineae, and the latter in turn attach to papillary muscles (Figure V-54) The extra opening probably has competent valvular function, and the condition has more interest from a developmental than from a pathologic point of view.

The subject of double mitral orifice was discussed at great length by Wimsatt and Lewis (1948) under the designation of *duplication of the mitral valve* These authors, who described a double orifice of the mitral valve in a yak calf, stated that a search of the literature revealed 14 well defined cases of the same condition in man. They related that in nine of the 14 human cases one of the two mitral ostia was smaller than the other and with two exceptions the smaller opening lay ventral to the larger opening. In five cases the two ostia were of approximately the same size.

The two authors, Wimsatt and Lewis, stated that they were unable to reach an agreement as to the developmental basis for the double mitral orifice in their heart of the yak. They differed as to the funda-

mental nature of the accessory mitral orifice. For this reason each of the two authors presented his own views in a separate discussion in their paper. Wimsatt held that the accessory mitral orifice was not an opening in one of the mitral leaflets but that it resulted from bisection of the mitral orifice into two distinct orifices. The cause for this supposed bisection of the mitral orifice was given as an abnormal fusion between the anlagen of the medial and lateral mitral leaflets. The reader will understand this assumption better by referring to Figure II-17D in the chapter on *Development of the Heart*. In the interpretation of Wimsatt as to the basis for double mitral orifice, he assumes that an abnormal bridge of tissue had passed across the left atrioventricular orifice and that this bridge had joined the lateral and medial mitral valvular primordia. If the interpretation of Wimsatt is correct, it is obvious that each of the two openings represents part of the mitral orifice rather than that one opening represents the true mitral orifice and the other an opening in one of the mitral leaflets.

In the same paper Lewis has expressed a different view as to the developmental basis for double mitral orifice. He would set the basis for the abnormality at an earlier stage in development of the heart, represented by that portrayed in Figure II-17C. Lewis believed that the accessory opening represented persistence of part of the embryonic common atrioventricular canal. In Figure II-17 the stages in the division of the common atrioventricular canal into mitral and tricuspid orifices are portrayed. The division of the common canal into right and left atrioventricular orifices depends upon the fusion in the midline of the heart of the ventral and dorsal endocardial cushions. In Figure II-17C fusion of the ventral and dorsal atrioventricular endocardial cushions is almost complete. At this stage, however, the right and left extremities of the dorsal and ventral cushions each have a prominence called a tubercle. If the left tubercle of the dorsal cushion should join the left tubercle of the ventral cushion before the remainder of the two cushions has joined completely, an opening would be present in the tissue which is destined to develop into the anterior mitral leaflet. Persistence of this opening, Lewis considered, would explain the accessory opening in the mitral valve. The accessory opening would thus represent a persistence of part of the common atrioventricular canal.

Lewis summarized his discussion of the developmental basis for double mitral orifice by stating. "In concluding that double mitral valves usually result from incomplete fusion of the endocardial cushions, the possibility of an adhesion of one or both tubercles across the mitral cleft is conceded." Shaner in 1949 stated that "the explanation favored by Lewis seems more probable, but that of Hartmann (1937) and Wimsatt is not impossible."

The exact developmental basis for double mitral orifice must, therefore, be left as controversial for the present.

The discussions of Wimsatt and of Lewis on the developmental basis for double mitral orifice in the yak are applicable to man both as to double mitral and as to double tricuspid orifice. According to these authors, double orifice of the tricuspid valve is of even less frequent occurrence than double mitral orifice. It is probable, however, that minor degrees of this condition are not uncommon in the tricuspid valve. In hearts otherwise normal the author has, on a number of occasions, seen small openings in the septal leaflet of the tricuspid valve surrounded by attachments of chordae tendineae. The author has encountered two cases of double orifice of the tricuspid valve associated with papillary muscles related to the accessory orifice. One of these cases is

reproduced in Figure V-54 Schraft and Lisa (1950) described an instance of an accessory opening of the anterior leaflet of the mitral valve as an incidental finding in a 54-year-old man

MALFORMATIONS OF THE SEMILUNAR VALVES



Figure V-55 *Isolated pulmonary* stenosis with patent foramen ovale in a man aged 26 years who died of cerebral abscess. The pulmonary trunk has been cut across and the pulmonary valve is viewed from above The valve is represented by a cone-shaped structure projecting superiorly into the pulmonary trunk Three raphe radiate from the central part of the cone to the wall of the pulmonary trunk The opening in the pulmonary valve is considerably narrower than the caliber of the pulmonary trunk which is of normal width (From Parker, R L, 1948 Reproduced by permission of the author and the W B Saunders Company)

Isolated Pulmonary Stenosis

When pulmonary stenosis or atresia occurs in association with a closed ventricular septum, a condition known either as *isolated* or *pure pulmonary stenosis* or *atresia* exists. Since stenosis differs clinically and pathologically from atresia, it is important to distinguish the two conditions. Pulmonary stenosis will be described first.

The essential and primary anatomic disturbance in *isolated pulmonary stenosis,* as the name implies, is in the pulmonary valve. The pulmonary valve is represented by a dome-shaped or conical fibrous funnel which projects superiorly into the pulmonary trunk. At the summit of the dome there is a narrow opening rarely more than several millimeters in diameter. This is the *only opening at the level of the pulmonary valve.* The narrow state of the opening in the dome is in striking contrast to the diameter of the pulmonary trunk at this level (Figure V-55). The width of the latter may equal or exceed the normal (Greene and associates, 1949) (Figure V-56) Regardless of the wide diameter of the pulmonary trunk, there exists a severe degree of pulmonary stenosis, since the narrow opening in the dome-shaped membrane which is the pulmonary valve is the



Figure V-56 Roentgenogram of the thorax in a man aged 26 years with isolated pulmonary stenosis The pulmonary valve is illustrated in Figure V-55 (Other illustrations of the heart in this case appear in Figure V-57) The shadow of the pulmonary "conus" is prominent The apex of the heart lies above the diaphragm. (From Parker, R L, 1948 Reproduced by permission of the author and the W. B Saunders Company)

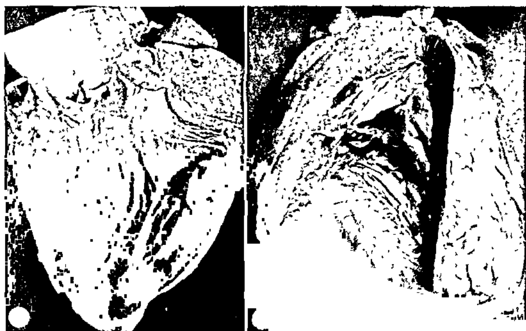


Figure V-57 Isolated pulmonary stenosis in a man aged 26 years whose pulmonary valve and roentgenogram of the thorax are illustrated in Figures V-55 and 56, respectively.
a The left ventricle and aorta The ventricular septum is intact and the aorta arises in a normal manner from the left ventricle The left ventricular wall is of normal thickness.
b The right ventricle The wall shows considerable concentric hypertrophy which may reduce the size of the chamber The probe lies in the outflow tract of the right ventricle This tract is narrow, probably secondarily to the concentric hypertrophy of the ventricular wall.
(Edwards, J E *Arch Path*, *61*.1103-1137, 1950)

only opening in the pulmonary arterial channel at valve level.

Probably in no other type of congenital cardiac malformation is there a greater similarity between one specimen and the next When viewed from above, the dome reveals that there are three raphae which extend from the central perforation in it, along its superior surface to the wall of the pulmonary trunk (Auerbach and Harper, 1947; Currens and associates, 1945, Blackford and Parker, 1941). These raphae probably represent locations at which division of one cusp from another should have occurred In only a rare case is there a minor difference in the appearance of the valve; instead of three raphae there are four.

The first case of Selzer and associates (1949) is such an example, and in one of three cases of isolated pulmonary stenosis in the Mayo Clinic pathologic collection there are four raphae in the stenotic pulmonary valve. These minor anatomic differences do not alter the basic nature of the deformity.

In isolated pulmonary stenosis, by definition, the ventricular septum is normally formed (Figure V-57*a*). The right ventricle shows a distinctive feature of severe hypertrophy of the concentric type. As a consequence of this hypertrophy, the right ventricular chamber appears to be smaller than normal This feature is particularly noticeable in the subpulmonary region, where the outlet of the right ventricle may be but a few millimeters in diameter (Figure V-57*b*). It is still unsettled whether the narrow condition of this part of the right ventricle is congenital or acquired. I am of the opinion that it is acquired secondarily to the hypertrophy caused by the severe degree of pulmonary stenosis.

Wood's case (1942) was exceptional in

that the right ventricle was relatively small but the left ventricle was greatly enlarged. This probably resulted from a great right-to-left shunt across an atrial septal defect.

The narrow state of the right ventricular outflow tract and its possible occurrence early in life are of practical importance Brock (1948) has advocated the performance of pulmonary valvotomy in cases of isolated pulmonary stenosis It should be recalled, however, that even after an ideal operation had been performed on the valve to relieve the stenosis, possible subpulmonary stenosis could still prevent a favorable result. Blalock and Kieffer (1950) reviewed the history of pulmonary valvotomy for this condition and summarized their surgical experience.

In cases of isolated pulmonary stenosis, the tricuspid valve is often described as thickened with fibrous tissue along the line of closure and at the points of attachment of the chordae tendineae (Auerbach and Harper, 1947) This feature seems adequately explained by the great stress that is placed upon the tricuspid valve during systole. The stress results from the fact that in isolated pulmonary stenosis the right ventricular systolic pressure far exceeds the systolic pressure of the right ventricle under normal conditions. The fibrous changes in the tricuspid valve may, therefore, be considered as a natural reaction to the excessive physical stresses placed on this valve.

The condition of the atrial septum varies Some hearts show an anatomically closed foramen ovale, others a patent foramen ovale (Saundby, 1877) (Plate V-1c and *d*). Selzer and co-workers have emphasized the importance of distinguishing cases of isolated pulmonary stenosis with patent foramen ovale from those in which the atrial septum is closed It is important to make this distinction, for when the atrial septum is closed there is no opportunity for recirculation of venous blood through the greater circulation; while in a patent foramen ovale, evidence may be seen of venous blood entering the left side of the heart (Brown and McCollum, 1950, Engle and Taussig, 1950).

The foramen ovale, when patent, appears similar to the foramen ovale in the fetus When the heart is viewed from within the left atrium the valve of the foramen ovale is usually seen properly formed This valve prevents the escape of left atrial blood into the right atrium but allows right atrial blood to enter the left atrium. Patency of the foramen ovale accounts for the possible finding of reduced oxygen concentrations in the arterial blood of persons with isolated pulmonary stenosis and, by the same token, allows cyanosis to appear before cardiac failure becomes manifest When the foramen ovale is closed, there is no opportunity for venous blood to enter the greater circulation and consequently cyanosis is not present during the period when the patient has adequate cardiac compensation

In the presence of isolated pulmonary stenosis a patent foramen ovale appears to be somewhat more common than a closed foramen ovale In the review of Selzer and associates there were 29 cases of isolated pulmonary stenosis with patent foramen ovale and 23 with closed foramen ovale.

Reference has already been made to the great disparity between the diameter of the pulmonary trunk and the opening in the pulmonary valve At times this disparity results entirely from stenosis of the pulmonary valve In other cases there appears to be a true dilatation of the pulmonary trunk (Blackford and Parker, 1941; Greene and associates, 1949) There seems to be no adequate explanation for generalized dilatation of the pulmonary trunk in such cases. Certainly it cannot be explained on the basis of pulmonary hypertension, for the pressure within the pu

monary trunk is characteristically low. During systole the blood within the right ventricle is under considerable pressure, but when the blood passes through the stenotic orifice into the wide pulmonary trunk the pressure shows a prompt and precipitous fall.

It is possible at times to see morphologic evidence of the force of the stream of blood which passes through the pulmonary valve The pulmonary trunk or one of its branches near the bifurcation may show a raised area which on microscopic examination is seen to be composed of fibrous tissue. Such a lesion is similar to the regurgitant pockets in the endocardium in cases of valvular insufficiency and in the intima of the left pulmonary artery opposite the mouth of a patent ductus arteriosus. My colleagues and I have called such lesions "jet lesions." To the morphologist the finding of such lesions indicates that an abnormal current had existed during life.

Few observations on the bronchial arteries have been reported in cases of isolated pulmonary stenosis These vessels have been described as dilated in cases of isolated pulmonary stenosis with patent foramen ovale by Vandam and co-workers (1947) in a girl aged 17 years, and by Selzer and associates in a man of 39. We have made similar observations in a man aged 26 years (Figure V-58). Doubtless many more such cases will be described as interest increases in collateral circulation to the lungs in cases of pulmonary stenosis. We are not aware that dilated bronchial arteries have been described in cases of pulmonary stenosis with closed atrial septum. The functional benefit of a collateral supply to the lungs in cases with open foramen ovale in which venous blood enters the arterial side of the circulation is understood, though the mechanism for the development of such collaterals is not clearly evident.



Figure V-58. Dilated bronchial arteries in the case of isolated pulmonary stenosis, illustrated in Figures V-55, V-56 and V-57 The mediastinal structures and the adjacent portions of the lungs are viewed dorsally The right bronchial artery arises from the aorta, ascends, courses behind the esophagus, and then proceeds inferiorly in a tortuous manner to the hilus of the right lung The left bronchial artery passes horizontally from the aorta to the hilus of the left lung It courses at a level corresponding to the inferior aspect of the left bronchus.

The stimulus for enlargement of the collateral vessels may be provided by the low pulmonary blood pressure that exists in this condition.

Characteristically, the studies on *cardiac catheterization* show a striking disproportion between the right ventricular and pulmonary systolic blood pressures (Greene *et al.*, 1949, Dow *et al.*, 1950). Whereas the pulmonary systolic blood pressure is below normal, the right ventricular pressure is profoundly elevated. In certain cases the right ventricular pressure may exceed the brachial arterial blood pressure (Pollack *et al.*, 1948).

On the basis of the appearance of the stenotic orifice, pulmonary insufficiency would be an anticipated additional finding in this condition. Indeed this is supported by the occasional observation of a diastolic murmur in the pulmonary area in a clinical case. That the volume of the re-

gurgitant blood is probably never great seems a justifiable interpretation, since the difference between the low pulmonary pressure and the right ventricular diastolic pressure is not great.

It appears that the ductus arteriosus closes normally in patients with isolated pulmonary stenosis, though in a rare case it is found patent at the time of necropsy, as in the patient of Rossman (1942), an infant girl four months old

The patient of Gordon and Perla (1931) was a boy of 13 years with isolated pulmonary stenosis and a patent ductus arteriosus There was complicating bacterial endarteritis involving the left pulmonary artery, the pulmonary trunk and the pulmonary opening of the ductus, but not the pulmonary valve A similar case, that of a boy aged five years, was studied by means of cardiac catheterization by Taylor and DuShane (1950).

It is pertinent to suggest that the rare combination of isolated pulmonary stenosis and patent ductus arteriosus is one that would seem particularly vulnerable to the development of bacterial endarteritis of the left pulmonary artery This tendency may be explained as follows In ordinary patent ductus arteriosus the development of bacterial endarteritis seems to start usually on that part of the wall of the left pulmonary artery traumatized by the jet of blood flowing from the aorta through the ductus arteriosus into the pulmonary arterial system When isolated pulmonary stenosis is added to patent ductus arteriosus the low pulmonary blood pressure characteristic of pulmonary stenosis causes a greater disproportion between the aortic and pulmonary blood pressures than when no pulmonary stenosis exists. The effect of this accentuated difference in pressures would make the traumatic effect of the shunted blood greater than in ordinary patent ductus arteriosus.

The development of bacterial endocarditis upon the stenotic pulmonary valve is uncommon. It occurred in the patient of Tuley and Moore (1917), a boy of 13 who died of the complicating infection. In this case it is conceivable that the infection began at the site of a jet lesion in the pulmonary trunk and extended to involve the pulmonary valve secondarily. In McPhedran's (1924) patient, a man of 23, bacterial endocarditis seemed to have arisen on the tricuspid valve and to have involved the pulmonary valve secondarily Abbott, Lewis and Beattie (1923) reported similar pathologic findings in a girl aged 14 years.

Cerebral abscess may complicate those cases of isolated pulmonary stenosis without bacterial endocarditis but with associated patent foramen ovale Parker (1948) reported this complication in a man of 26 who was seen at the Mayo Clinic. It is of interest that in cases with closed atrial septum this complication apparently does not develop. In their review Selzer and associates (1949) listed three instances of cerebral abscess among cases of isolated pulmonary stenosis with patent foramen ovale but no instance among the cases with closed atrial septum This seems to support the concept that the syndrome of congenital cardiac disease and cerebral abscess occurs only when there is an opportunity for venous blood to by-pass the lungs and to enter the arterial system directly

The major causes of death in isolated pulmonary stenosis are cardiac failure, bacterial endocarditis or endarteritis and cerebral abscess Abbott, Lewis and Beattie reported that among 19 cases of isolated pulmonary stenosis analyzed, the average duration of life was 21.3 years. The extremes of age among this group of cases were four years and 57 years. These figures are in striking contrast to those concerning survival in cases of isolated pulmonary atresia In the latter condition death usually occurs during early infancy.



Figure V-59 Isolated pulmonary atresia in a male infant four months of age

a The pulmonary valve viewed from above The orifice is closed by a fibrous membrane from the center of which three raphae radiate to the wall of the pulmonary trunk

b The right side of the heart The right ventricular cavity is diminutive. Its size is in profound contrast to the great thickness of its wall

c. The tricuspid valve, though small, appears normally formed

Isolated Pulmonary Atresia

This condition must be distinguished from isolated pulmonary stenosis, since the clinical course and the pathologic features in these two conditions vary considerably. The patient with isolated pulmonary stenosis usually lives to adolescence or adult life, whereas the patient with isolated pulmonary atresia rarely, if ever, lives beyond infancy A summary of the features of isolated pulmonary stenosis has been given in the preceding section.

In isolated pulmonary atresia, as in isolated stenosis, the malformation lies in the pulmonary valve and is responsible for associated and secondary changes. In isolated pulmonary atresia the pulmonary valve is closed by a fibrous diaphragm. When viewed from above, the diaphragm appears to be formed by a fusion of three cusps. Radiating from the center of the diaphragm are three equidistant ridges (Figure V-59*a*). These extend to the wall of the pulmonary trunk or end at the junction of the fused cusps with the arterial wall. The three ridges are similar in appearance to the three ridges or raphae usually seen in the superior aspect of the fused cusps in cases of isolated pulmonary stenosis. As already indicated, in pulmonary atresia there is no opening within the fibrous membrane representing the fused pulmonary cusps. This is the crucial point by which isolated pulmonary atresia is distinguished from isolated pulmonary stenosis. The function of the heart and the secondary pathologic features depend on whether or not there is an opening, however small, in the pulmonary valve.

Below the atretic pulmonary valve the right ventricular chamber is found to be minute but the right ventricular wall is greatly hypertrophied, measuring as much as 2 cm. thickness in infants. When the right ventricular chamber is exposed, the appearance has been compared to that of a peach from which a segment of the fruit and the stone have been removed; the former position of the stone being represented by the ventricular chamber and the substance of the fruit by the hypertrophied ventricular wall (Figure V-59*b*).

The ventricular septum is completely formed, and the tricuspid valve, although diminutive, usually appears properly

formed (Figure V-59*c*). I have felt that the combination of pulmonary atresia, a closed ventricular septum and a normally functioning tricuspid valve are the underlying factors in the tremendous right ventricular hypertrophy. It would seem that while some blood could enter the ventricle during diastole, none could escape as long as the tricuspid valve remains competent The result would be that during each systolic contraction the right ventricle would be contracting against a noncompressible substance and this factor would result in marked hypertrophy of its wall This assumption seems to be supported further by those cases of pulmonary atresia in which there is also a closed ventricular septum but an atretic tricuspid valve (see Tricuspid Atresia, Type Ia, page 377) In the latter condition, in which no blood can enter the right ventricle, the chamber is tiny and its wall is so small as to be easily overlooked at necropsy (Figure V-45*a*). Unless sections are taken from appropriate locations and studied microscopically to determine the presence of a cardiac chamber, one may at times be unable to demonstrate the right ventricle with confidence

In cases of isolated pulmonary atresia the right atrium cannot empty itself through the route of the tricuspid orifice There is always a communication between the two atria through the atrial septum (Figure V-60) Usually this communication takes the form of a patent foramen ovale, similar in appearance to the patent foramen ovale of the fetus and newborn Thus, as in tricuspid atresia, all the blood which enters the right atrium through the venae cavae and the coronary sinus is directed into the left atrium Here it is met by oxygenated blood entering the left atrium by way of the pulmonary veins The left atrium is thus, functionally, a single atrium. This chamber communicates normally with the left ventricle through the mitral valve It has been seen that in cases of isolated pulmonary stenosis a communication between the two atria is not necessary for the circulation to be maintained When there is such a communication, venous blood may enter the arterial side of the circulation. Thus in isolated pulmonary stenosis, the presence of an interatrial communication is not only non-essential, but probably disadvantageous. In cases of isolated pulmonary atresia, on the other hand, an interatrial communication is necessary to allow the blood to circulate through the heart.

Just as the left atrium functions as a single atrium, so does the left ventricle function as a single ventricle Its chamber has a large capacity and its wall, while not as thick as the greatly thickened right ventricular wall, nevertheless is thicker than normal. The aorta is in normal communication with the left ventricle and is properly related to the pulmonary trunk The great vessels are not transposed The aorta is somewhat wider than normal while the pulmonary trunk is narrower. In spite of the atresia of the pulmonary valve, the pulmonary trunk, while reduced in caliber, may have a moderate diameter The ductus arteriosus is usually found open and through it the lungs receive the major part of their blood The diameter of the patent ductus arteriosus is probably always inadequate to carry an optimal amount of blood to the lungs, and when the ductus arteriosus undergoes involutional changes which ordinarily lead to obliteration of its lumen, the effect of the diminishing blood flow to the lungs may be responsible for death before actual closure is effected.

The survival time of patients with isolated pulmonary atresia is short.

In 1886 Leo reported this condition in a girl who had died at the age of eight months He stated that 14 other cases of the condition had been reported up to the time of his paper. Leo stated that, with the exception of Hare's patient, who died

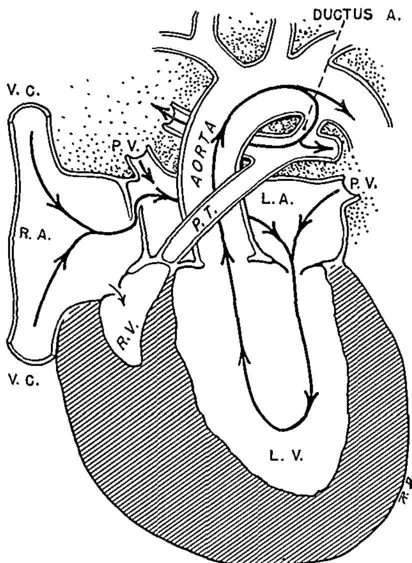


Figure V-60 The intracardiac circulation in isolated pulmonary atresia. Since there is no way for blood to leave the right side of the heart, the circulation is essentially like that in tricuspid atresia, Type Ia. (See Figure V-45*a*)

at the age of nine months, the patients whose histories were reviewed died in the neonatal period.

Similar observations on length of life in cases of this malformation were made subsequently by Abbott, Lewis and Beattie (1923). These authors analyzed the reports of 83 cases of pulmonary stenosis and atresia. In six of these cases isolated pulmonary atresia was present. Each of the patients showed intense cyanosis during life and each died at an early age, the ages at death varying from six days to six months. The average age at death was 16 weeks. Fortunately, isolated pulmonary atresia is to be classed as a rare cardiovascular malformation.

It seems appropriate to consider the developmental basis for isolated pulmonary stenosis and isolated pulmonary atresia together. That isolated atresia is a congenital malformation is not doubted, but isolated pulmonary stenosis has at times been considered as an acquired lesion. In my opinion each is a congenital malformation. Moreover, isolated atresia is prob-

ably an accentuation of the valvular malformation seen in cases of isolated stenosis It seems correct to assume that these valvular deformities develop relatively late in embryonic life, at least after the membranous portion of the ventricular septum has formed. If the stenosis or atresia developed earlier, it is conceivable that the interventricular foramen would fail to close.

Neither of the types of valvular malformations being considered can be accepted as an arrest of development, since the embryo has no stage in its development which can be taken as the morphologic counterpart of the valvular structure seen in either of the conditions under consideration It is logical, then, to assume that after the valvular primordia have formed, abnormal fusion between them has taken place Some authors consider such fusion to be caused by fetal endocarditis, but conclusive proof for such a claim is wanting

Rossman (1942) reported on histologic studies of the heart in his case of isolated pulmonary stenosis, in which the patient was a child aged four months He found no evidence of inflammation in the myocardium or in the valves, including the pulmonary valve. The mural endocardium of the subpulmonary portion of the right ventricle showed some fibrous thickening The latter change is consistent with a reaction to the trauma which occurs in the mural endocardium proximal to a stenotic or atretic valve. In older patients with isolated pulmonary stenosis there may be fibrous thickening and vascularization of the stenotic pulmonary valve. Such changes are no proof of fetal endocarditis since they may be the result of inflammation acquired by the stenotic valve after birth. They may also represent a reaction to the damage caused by the propulsion of blood by the right ventricle against the stenotic valve.

Isolated Aortic Atresia. Coexistent Aortic and Mitral Atresia

In isolated aortic atresia (Figure V-61*a*) and in coexistent aortic and mitral atresia (Figure V-61*b*) the appearances of the aortic valve are similar The orifice is closed by a fibrous diaphragm (Canton, 1849) similar in appearance to the atretic

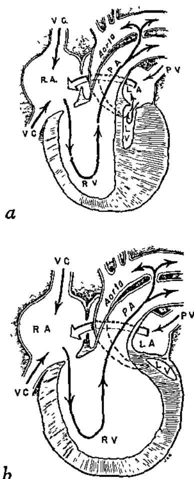


Figure V-61. *a* The intracardiac circulation in isolated aortic atresia The left ventricle, although having a small chamber, has a greatly thickened wall (From Edwards, J E, *Postgrad Med*, 3 327-341, 1948 Reproduced by permission of *Postgraduate Medicine*)

b The intracardiac circulation in coexistent aortic and mitral atresia. The left ventricular chamber is diminutive and is hidden in the wall of the single functioning right ventricular chamber

pulmonary valve in cases of isolated pulmonary atresia. The obstructing diaphragm, when viewed from above, usually shows three raphae which radiate from the center of the diaphragm to its periphery and end at the aortic wall (Figure V-62*a*) The coronary ostia lie superior to the membrane In each condition the ventricular septum is intact. Except for the appearance of the left ventricle and the mitral valve, the two conditions show the same secondary phenomena.

In coexistent aortic and mitral atresia the left ventricular chamber is tiny (Walker and Klinck, 1942), and its wall is so thin as to escape detection, at times, unless microscopic sections taken from appropriate locations are studied (Figure V-61*b*). The left ventricle in this condition is similar to the right ventricle in cases of coexistent pulmonary and tricuspid atresia, the latter are designated in this chapter as tricuspid atresia, Type Ia

Some cases reported as examples of aortic and mitral atresia with a single ventricle are probably examples of the malformation under consideration. Inasmuch as the left ventricle is a chamber without any function, the malformation has been given the name *cor pseudotriloculare* (Dolgopol, 1934).

Soloff (1949) described the case of an infant boy two weeks of age whose electrocardiogram showed left axis deviation. There was atresia of the aortic and mitral orifices, a narrow ascending aorta and a patent ductus arteriosus through which the systemic arterial system received blood. The ventricular part of the heart was described as possessing a large right ventricle, and a small left ventricle communicating freely with the right ventricle. In a case such as this, one must consider the possibility that the chamber, believed to be a left ventricle, in fact represented a portion of the trabeculated right ventricle, and that the true left ventricle lay in the wall of the large right ventricle and was unrecognized. Taussig (1945) reported a case of coexistent aortic and mitral atresia (Case 2) in which the subject was a male infant aged five days, and in which no trace of the left ventricle could be found.

In contrast to the situation in coexistent aortic and mitral atresia in which the left ventricle is diminutive, in isolated aortic atresia the left ventricular cavity is small but its wall is greatly thickened (Figures V-61*a* and 62*b*) (Wenner, 1909, Case 7). This feature is similar to the great thickness of the right ventricular wall when there is pulmonary atresia coupled with a closed ventricular septum and a patent tricuspid orifice (see Isolated Pulmonary Atresia, page 398). This thickness apparently is caused by contraction of the ventricle against blood caught in the chamber as a result of the aortic atresia and a functioning mitral valve.

In cases of isolated aortic atresia or of coexistent aortic and mitral atresia the left atrium may be normal in size or smaller or larger than normal. Since there is no normal outlet from the left side of the heart, an unusual route must be present for the exit of blood from the left atrium. In this connection the situation with respect to flow of blood from the left atrium is identical to that existing in cases in which mitral atresia is the basic malformation. The thebesian veins in the atrial septum may be wider than normal and so carry blood from the left atrium into the right. This route, however wider than normal it may be, is never sufficient to carry a considerable amount of blood.

If life after birth is maintained, there is a larger interatrial communication. At times this takes the form of an atrial septal defect, represented by a short valve of the foramen ovale, as in the second case of Willer and Beck (1932). More commonly there is patency of the foramen ovale for



Figure V-62 Isolated aortic atresia in a female infant four months old. (Reported by DuShane, J. W *M Clin North America*, 32 879-894, 1948, Case 2)

a The ascending aorta has been opened, and the aortic valve is seen from above There is a membrane closing the valve orifice Three raphae radiate from the center of the diaphragm to the aortic wall

b The left ventricular wall is greatly thickened. The chamber is small The mitral valve is normally formed, but small Prominent thebesian veins are seen in the atrial septum

c The right side of the heart The right atrium is greatly dilated A probe lies in the small opening which is a patent foramen ovale The right ventricular chamber is dilated and its wall is hypertrophied

d The great vessels and the exterior of the heart The pulmonary trunk is widely patent and is correctly related to the hypoplastic ascending aorta A patent ductus arteriosus connects the pulmonary arterial system with the aorta (From DuShane, 1948 Reproduced by permission of the author and the W B Saunders Company.)

another reason. Evidently as a result of the great pressure which is built up in the left atrium, the anterior aspect of the valve of the foramen ovale is forced through the foramen ovale into the right atrium. In this way an atrial septal defect is created. Though this seems to be the usual basis for interatrial communication in these cases, the opening is often described merely as a "patent foramen ovale." It should, however, be recognized as a peculiar form of patency It is similar to the usual patent foramen in cases of mitral atresia

In the case of isolated aortic atresia reported by Bellet and Gouley (1932), the patient was an infant who died 12 hours after birth and showed a prematurely closed foramen ovale. The left atrium presented the openings of four pulmonary veins at its dorsal aspect and ventrally another venous connection Because the permission for necropsy allowed only examination of the heart, the termination of the last-named vessel could not be determined. The authors suggested with correct reasoning that it might have been an anomalous vein similar to that in the case of McIntosh (1926). In the latter case, one of mitral atresia and premature closure of the foramen ovale, there was an anomalous channel between the left atrium and the superior vena cava. Through such a channel blood could leave the left atrium and so eventually reach the right atrium. A fuller discussion of the case of McIntosh and of similar cases will be found in the sections on Mitral Atresia and on Malformations of the Great Veins (see pages 387 and 496).

In a review of the literature, Ruge (1905) found that the foramen ovale was closed in five of 50 cases of congenital aortic atresia. The author stated that, while fetal life is possible in such cases, postnatal life is not. Unless an unusual vascular connection exists, such as that suggested by Bellet and Gouley, the statement of Ruge is entirely justified.

In cases of isolated aortic atresia or of coexistent aortic and mitral atresia all the blood coming to the left atrium by way of the pulmonary veins flows eventually into the right atrium The right atrial chamber is dilated, for within it is collected not only the arterialized but also the venous blood returning to the right atrium through normal channels. Moreover, since the right ventricle likewise receives and propels all the blood which circulates through the heart, the right ventricle is dilated and hypertrophied (Figure V-62*c*). The right ventricular hypertrophy accounts in large measure for the increase of weight characteristic of hearts with coexistent aortic and mitral atresia. In cases of isolated aortic atresia some of the increase of cardiac weight is accounted for by the right ventricular hypertrophy and some by the great thickness of the left ventricular myocardium.

In both the conditions named, all the blood which flows out of the heart passes into the pulmonary trunk, thus explaining the great dilatation of the pulmonary trunk (Figure V-62*d*). The systemic circulation receives its blood by way of a patent ductus arteriosus. It is apparent that the blood to the branches of the aortic arch and to the coronary arteries flows in the reverse direction from normal, that is, toward the heart. While the arch of the aorta is of normal size, the ascending aorta is materially narrower than normal and is often described as hypoplastic (Figure V-62*d*). There is no transposition of the great vessels. At times hypoplasia of the ascending aorta is called stenosis. This term is not recommended for this condition, since it implies that there is a zone of vascular narrowing which interferes with passage of a sufficient amount of blood. In this instance the ascending aorta functions merely as a channel leading to the

coronary arteries and for this purpose it is an adequate channel. The hypoplasia probably results from the relatively small amount of blood which the ascending aorta carries. Brown (1939) has expressed the opinion that coronary insufficiency may be present. Though this statement cannot be supported on the basis of existing evidence, it cannot be categorically denied

Figure V-63 is the roentgenogram of the heart illustrated in Figure V-62

The gross vascular arrangements in cases of aortic atresia would suggest that there would be no problem in obtaining adequate pulmonary blood flow Certainly the wide pulmonary arteries would constitute no barrier. The usual narrow state of the interatrial communication, however, must create a barrier to pulmonary venous emptying and this must be reflected in an increased resistance to blood flow through the lungs. It is conceivable that this resistance may equal or exceed the resistance to systemic blood flow. Under such circumstances a substantial portion of the blood flowing in the pulmonary trunk would tend to escape through the ductus arteriosus into the aorta rather than flow predominantly through the pulmonary arteries Thus in isolated aortic atresia and in coexistent aortic and mitral atresia, while there is no anatomic stenosis in the pulmonary arterial system, there may be a barrier to pulmonary blood flow created by interference with pulmonary venous drainage This is probably the basis for cyanosis, so common in the clinical course of patients with these defects. In 1948 the author suggested that this condition might be alleviated by surgical enlargement of the interatrial opening



Figure V-63 Roentgenogram of the thorax in the case of isolated aortic atresia illustrated in Figure V-62 The prominent shadow at the left side of the base of the heart is reminiscent of a similar shadow in the roentgenogram of a case of mitral atresia illustrated in Figure V-53 (From DuShane, J. W. *M. Clin North America*, 32.879 894, 1948, Case 2 Reproduced by permission of the author and the W. B Saunders Company)

The developmental basis for aortic atresia is not established. In view of the intact nature of the ventricular septum it is assumed that the valvular malformation is formed relatively late in the period of cardiac development. Some (Abbott, 1936, Farber and Hubbard, 1933) have suggested that the atresia represents the end stage of fetal endocarditis, but this is not proved Microscopic examination of the myocardium in the cases reported by von Haam and Hartwell (1939) and by Rossman (1942) has failed to show any evidence of inflammation.

In Rossman's case, one of isolated aortic atresia, both the aortic and mitral valves, upon histologic examination, were thin layers of connective tissue without inflammatory exudates or scars. On the other hand, Willer and Beck (1932) in two cases of isolated aortic atresia, found attached to the obstructing diaphragm vascular connective tissue including macrophages that contained hemosiderin. Though they claimed that these features were evidence of endocarditis, it is possible that the tissue they described represented an organi

thrombus It would be no surprise to find a thrombus forming at the blind end of the aorta just superior to the atretic valve. Willer and Beck found no evidence of inflammation in the myocardium in a histologic study of their cases.

In isolated aortic atresia there is often great thickening with elastic tissue of the left atrial and left ventricular mural endocardium and myocardial scarring (Wigglesworth, 1936, Rossman). In coexistent aortic and mitral atresia the left atrial endocardium is similarly thickened Some have sought to explain this change as representing the end result of fetal endocarditis which, in addition to causing the mural endocardial change, had been responsible for the valvular atresias (von Zalka, 1924) Others have considered that the fibrous thickening of the mural endocardium is merely the result of the mechanical stresses incident to the obstruction at valve level (Strassny, 1901; Loeser, 1915) The latter interpretation seems the correct one. It is to be pointed out that the myocardial scarring usually lies immediately beneath the thickened endocardium (von Zalka) The scars of the myocardium are probably continuous with the thickened endocardial connective tissue Von Zalka observed that in cases of pulmonary atresia the right ventricular mural endocardium and underlying myocardium were scarred Similarly he observed that in cases of aortic atresia there was scarring of the left ventricular endocardium and myocardium He considered these observations to support the concept that the basis for the valvular atresia was inflammatory. This interpretation, however, does not seem to be correct, in fact, the observations of von Zalka concerning mural endocardial and myocardial fibrosis in chambers lying proximal to an atretic valve may be explained on a mechanical basis.

It is to be emphasized that cellular infiltration is rarely associated with the endocardial thickening and myocardial scarring (Isaacson *et al.*, 1946). In occasional cases there are many wide blood-containing channels in the myocardium of the left ventricle and atrium (von Zalka; Bellet and Gouley). In their case Bellet and Gouley could trace continuity of these sinuses with the smaller coronary arteries on one hand, and with the cardiac chambers on the other. Though these channels may represent persisting fetal myocardial sinusoids, they may also be dilated thebesian veins, the dilatation being incident to stenosis of the mouths of the veins by the thickened mural endocardium.

While it is difficult to prove an inflammatory basis for the aortic valvular atresia, it is likewise difficult to explain the malformation otherwise There is no stage in cardiac development which is characterized by anatomic closure of the aortic valve. For some occult reason there seems to be a secondary fusion of the developing valve cusps.

It does not appear appropriate to consider the malformation as resulting from unequal partitioning of the truncus arteriosus. As already explained, the disproportion in size between the ascending aorta and the pulmonary trunk seems to be a secondary phenomenon based upon the relative loads placed upon these two vessels by virtue of the basic malformation. Evidence supporting the concept that the atresia is not caused by unequal partitioning of the truncus is found in the presence of an intact ventricular septum and in the fact that the diaphragm which closes the aortic valve has elements which seem to represent three aortic cusps. In the section on malformations resulting from abnormal partitioning of the truncus arteriosus, it was seen that unequal partitioning of the truncus arteriosus results in a defect of the membranous portion of the ventricular septum, and that in malformations such as

the tetralogy of Fallot, the unequal partitioning of the truncus arteriosus results in a narrow pulmonary valve which is often bicuspid.

The incidence of aortic atresia is relatively low. In Abbott's (1936) 1000 cases there were 12 cases of aortic atresia. This presumably included cases of isolated aortic atresia and those of coexistent aortic atresia and mitral atresia. The incidence for some reason is much higher in the Mayo Clinic collection. Among 212 specimens with major cardiovascular malformations there are one case of coexistent aortic and mitral atresia and seven cases of isolated aortic atresia. One of these latter cases was contributed to the author by Dr James H Peers. One of the cases in this collection was reported by Wesson and Beaver (1935) and another by Baggenstoss (1940).

Few subjects with aortic atresia survive long after birth. Among 12 cases analyzed by Abbott only two patients lived more than one week after birth. One of these was the patient of Shattock (1881). Cyanosis developed at the age of nine days and the patient died at the age of 25 days. In the case of Summons (also quoted by Abbott), the patient lived to the age of 15 weeks.

In reviewing the subject of aortic atresia, Herxheimer (1910) found that many of the subjects die during fetal life. Of those who are born alive the duration of life is short, more than half of the patients dying during the first week of postnatal life. This author stated that survival was delayed for several weeks in some cases. The following list gives the names of authors who have reported such cases, with ages of their patients at the time of death: Thérémin, 22 days, Shattock, 25 days; Rauchfuss, 25 days; Meyer, 27 days; Fischer, six weeks, and the patient of Bardelebens, 27 weeks. The survival time in cases of aortic atresia studied at the Mayo Clinic is likewise low. Only one patient of seven with isolated aortic atresia lived four months. One died at one month of age and the remaining five patients died one to five days after birth. The subject in whom aortic and mitral atresia coexisted was a stillborn male.

There is a predominance of male patients. Five of the seven Mayo Clinic patients who had isolated aortic atresia were boys. Herxheimer noted that Rauchfuss found 14 boys and eight girls among 22 cases of aortic atresia. The predominance of the male sex is borne out by reports of cases in the more recent literature.

Most deaths are probably the result of insufficient pulmonary blood flow, the latter caused by unpaired pulmonary venous drainage.

Lev and Killian (1942) reported on two patients with isolated aortic atresia who had had first degree of atrioventricular block during life and prolonged QRS complexes. They made histologic studies of the conduction system. In the first patient, who lived 44 hours after birth, they found the atrioventricular node normal. The bundle of His was embedded in and partly penetrated by a large mass of scar tissue. The distal portion of the left branch of the bundle was encased in and partly subdivided by the hyalinized connective tissue of the left ventricular mural endocardium. The second case was essentially similar.

Bicuspid and Quadricuspid Semilunar Valves

Either of the semilunar valves may vary from the normal in that there is either a deficiency or an excess in the number of cusps. The most common of these variations is the one in which the aortic valve is bicuspid.

Bicuspid Aortic Valve. Whenever a bicuspid aortic valve is encountered, the question as to whether the abnormality represents a congenital malformation or an acquired deformity arises. For this

reason it is pertinent to review the criteria for distinguishing these two types of bicuspid aortic valve. Koletsky (1941*a* and *b*) has made comprehensive reviews on this subject. Much in this section is taken from his writings

Two types of congenital bicuspid aortic valves are found. *In one type the two* cusps are of equal size and there is usually no question that a malformation exists (Figure V-64*a*). In the second type, one of the two cusps is divided by a ridge or a raphe into two segments (Figure V-64*b*). The ridge lies vertically in the aortic wall

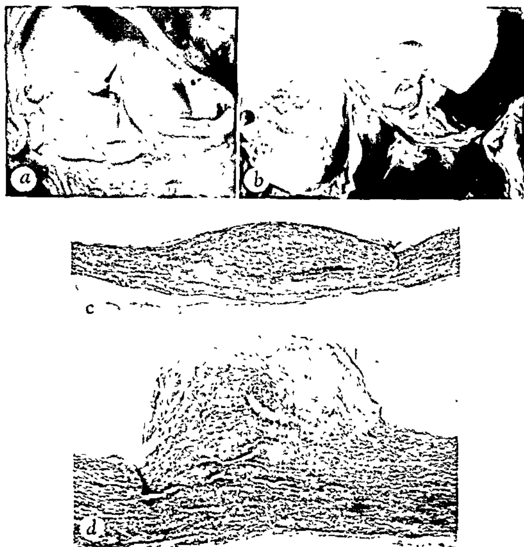


Figure V-64 *a* Congenital bicuspid aortic valve in which the two cusps are of about equal size No raphe is present

b *Congenital bicuspid aortic valve. A raphe extends from the aortic wall onto the dorsal* one of the two cusps.

c. Photomicrograph of section across the raphe in congenital bicuspid aortic valve. Aortic media extends uninterruptedly through and forms the raphe. Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. X 13.

d Photomicrograph of section across the raphe in acquired bicuspid aortic valve. The raphe is composed of collagenous tissue. The aortic media does not extend into it. Contrast with the picture of the congenital raphe illustrated in *c*. Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. X 14.

of the aortic sinus. It extends into the depths of the sinus and may then extend *onto the sinusal aspect of the conjoined* cusp. The conjoined cusp may be equal in size to the other cusp, but more commonly the conjoined cusp is the larger

Osler (1886) laid down certain gross criteria for the distinction between acquired and congenital bicuspid aortic valves. Subsequently, however, others (Lewis and Grant, 1923, Bishop and Trubek, 1936; Koletsky) have taken the view that use of the gross characteristics of a bicuspid aortic valve is unreliable in the differentiation between a congenital and an acquired bicuspid aortic valve Lewis and Grant reported that the microscopic characteristics of the raphe and of the neighboring aortic wall were the crucial points in making the distinction The work of these authors was confirmed and extended by Bishop and Trubek and by Koletsky A summary of the microscopic characteristics of the raphe and aortic wall in congenital and in acquired bicuspid aortic valve follows.

In congenital bicuspid aortic valve the upper part of the raphe is composed exclusively of aortic medial tissue covered by a thin layer of intima (Figure V-64*c*). At this level the elastic fibers of the outer media pass without interruption through the ridge and are parallel except in the central portion of the raphe. In the latter location the elastic fibers are whorled and irregular. In the base of the raphe, in the vicinity of the annulus fibrosus, the regular character of the raphe, resembling aortic media, is partly lost. Usually the annulus extends upward and divides the tissue of the raphe into two halves, one superficial and the other deep. Koletsky has compared the shape of the annulus to that of an inverted letter V, the apex of the V being covered by medial tissue of the aorta on each side. Superficial elastic fibers of the raphe may extend down to the attachment of the cusp

The important point to recall in this arrangement is that part of the aortic media lies superficial to, that is, toward the sinus of, the annulus fibrosus This arrangement is like that seen in the normal aortic wall at the *center* of the aortic sinus; whereas *at the commissure the relationship changes* and the *annulus fibrosus lies superficial* to the aortic media In contrast to the presence of aortic media superficial to the annulus fibrosus at a raphe of congenital type (Figure V-64*c*), at a raphe of the acquired type the annulus fibrosus and the aortic media have a normal commissural relationship, the aortic media lying deep to the annulus The acquired raphe thus contains no medial elements of the aorta (Figure V-64*d*) and is composed of the collagenous tissue of the annulus fibrosus overlain by the interadherent elements of the two cusps which have become fused to form, seemingly, one cusp Several strands of elastic tissue may be found in the acquired raphe, but these lack the regularity of the elastic fibers in the congenital raphe.

An acquired bicuspid valve results from inflammatory disease and may show cellular infiltration and vascularization of the raphe. In contrast the raphe in congenital bicuspid valve is devoid of inflammatory features.

Koletsky has reviewed the incidence of congenital bicuspid aortic valve. Among 3300 consecutive necropsies at the Institute of Pathology of the University Hospitals of Cleveland, he found 18 cases. McGinn (1936) determined that there were 10 instances of this malformation among 7500 necropsies at the Massachusetts General Hospital. Three instances of congenital bicuspid aortic valve were found among 13,115 necropsies which Leech (1935) reviewed. Gross (1937) re

ported an incidence of 28 specimens with bicuspid aortic valves among 5000 hearts.

None of these occurred in the younger age groups although 932 of the 5000 hearts were from persons less than 10 years of age. The average age of the 28 individuals with bicuspid aortic valves was 45 years In a special study made on 16 of these hearts, Gross concluded that in all of the cases the aortic valve was bicuspid on an acquired basis. It should be emphasized that in two of these cases the structure of the aortic annulus was like that in congenital bicuspid aortic valve, according to the criteria of Lewis and Grant, Bishop and Trubek, and Koletsky. Gross expressed the opinion that a bicuspid aortic valve in an adult should not be considered a congenital malformation unless other cardiac malformations coexist. This attitude seems unjustified in view of the apparently sound criteria for the distinction of a congenital from an acquired bicuspid aortic valve.

Congenital bicuspid aortic valve may exist as the sole malformation in a given case or it may be associated with other cardiovascular malformations

In Koletsky's (1941*a*) 18 cases of congenital bicuspid aortic valve, nine were encountered in infants and children and nine in adults In seven of the nine younger patients there were associated anomalies of the heart while in nine adults there were two with associated cardiac malformations. Associated cardiovascular malformations in Koletsky's series included transposition of the great vessels, ventricular septal defect, aneurysm of the ventricular septum, persistent ostium primum and, foremost, coarctation of the aorta. The latter malformation was present in four of the younger group and in one of the adults. In one patient, an eight-year-old boy, the congenital bicuspid valve was associated with coarctation of the aorta and an aneurysm of the circle of Willis. Rupture of the latter was the cause of death.

Though earlier authors have indicated a definite but relatively low incidence of bicuspid aortic valve in coarctation of the aorta, it seems correct to estimate that bicuspid aortic valve occurs in about 75 per cent of the cases of this aortic malformation (Edwards *et al.*, 1948). When associated with coarctation of the aorta, the bicuspid aortic valve may frequently be responsible for aortic valvular insufficiency (Christensen and Hines, 1948; Burchell, 1950).

When congenital bicuspid aortic valve is not associated with other cardiovascular malformations, it usually causes no functional disturbance but constitutes a hazard as a basis for the development of bacterial endocarditis.

Abbott (1925) reported that among 44 cases of bicuspid aortic valve 18 had become complicated by bacterial endocarditis. Though she accepted a congenital basis for all of the bicuspid valves, it is possible that in some cases the valvular deformity was present on an acquired basis. Lewis and Grant found that among 31 cases of subacute bacterial endocarditis in eight cases the infection started on an aortic valve that was congenitally bicuspid. In discussing these findings, Koletsky (1941*a*) stated that, as in a previously normal valve, the congenitally bicuspid valve may be complicated by rheumatic inflammation. The deformity so produced in the anomalous valve may have an influence of its own in making the valve susceptible to a complicating bacterial infection. Hoagland (1950) studied the cases of anomalous semilunar valves that were observed at necropsy at the Mayo Clinic from 1920 through 1943. Thirty-three examples of congenital bicuspid aortic valves were present. Of 25 of these cases, in which the subjects were adults, five were complicated by subacute bacterial endocarditis.

Gelfman and Levine (1942), in a study of 453 cases of congenital cardiovascular malformations, found that 181 of the patients were two years of age or older at the time of death Almost 29 per cent of the patients more than two years of age had a bicuspid aortic valve which was considered congenital in nature Eighty per cent of these were not associated with other cardiovascular malformations Bacterial endocarditis was encountered in 30 of the 181 cases of all cardiac malformations in which the patients were two years of age or older In 21 per cent of the 30 cases of bacterial endocarditis the infection occurred on congenitally bicuspid aortic valves.

Bicuspid Pulmonary Valve. While bicuspid pulmonary valves may exist in a pulmonary orifice of normal caliber and may be the sole malformation in a given heart (Figure V-65*a*), this condition is usually part of a serious form of cardiac malformation The most common malformation in association with bicuspid pulmonary valve is the tetralogy of Fallot (Dilg, 1883) Koletsky (1941*c*) has related that about one-third of the cases of bicuspid pulmonary valve are associated with the tetralogy of Fallot and, moreover, most hearts with the tetralogy of Fallot have a bicuspid pulmonary valve as part of the malformation Other malformations that may have an associated bicuspid pulmonary valve include complete transposition of the great vessels and tricuspid atresia In these conditons, however, the association of the valvular abnormality does not approach the high incidence seen in the tetralogy of Fallot

In Koletsky's (1941*c*) analysis of data on nine cases of bicuspid pulmonary valve there were two in which this was the sole malformation Three cases were associated with the tetralogy of Fallot, one case with a ventricular septal defect and



Figure V-65. *a* Congenital bicuspid pulmonary valve guarding a normal-sized orifice A raphe extends from the wall of the pulmonary trunk onto the posterior of the two cusps This was observed incidentally in a heart with no other malformations

b Quadricuspid aortic valve in which three of the cusps are of about equal size The fourth, toward the right of the illustration, is rudimentary.

c. Quadricuspid pulmonary valve One of the cusps is rudimentary.

one with cor triloculare biatriatum with transposition of the great vessels. Two of the cases were associated with bicuspid aortic valve. The latter phenomenon, according to Koletsky, is rare, only four other such cases having been recorded.

In a comprehensive analysis of the malformations of the semilunar valves observed at the Mayo Clinic from 1920 through 1943, Hoagland found in addition to the 33 cases with bicuspid aortic valve, seven with bicuspid pulmonary valve, five with quadricuspid aortic valves and 15 with quadricuspid pulmonary valves Of the seven cases of bicuspid pulmonary valve, six were associated with serious forms of congenital cardiac malformations, as follows: tetralogy of Fallot, three cases; complete transposition of the great vessels, two cases, and ventricular septal defect, one case. The seventh case, in which the patient was an adult, was associated with a congenital bicuspid aortic valve

Quadricuspid Aortic and Pulmonary Valves. Quadricuspid pulmonary valve, as indicated by the studies of Dilg (1883) and Hoagland, is at least three times as common as quadricuspid aortic valve. The four cusps may be of equal size; one of the cusps may be rudimentary and the size of the other three appear equal, and normal (Figure V-65*b*); or all of the cusps may vary in size (Figure V-65*c*). Usually neither of these semilunar valvular malformations is of functional significance, being discovered unexpectedly at necropsy.

In 1883 Dilg observed that there were, in the literature, 24 cases of quadricuspid pulmonary valve and only nine of quadricuspid aortic valve. This author also stated that there were two examples in which the pulmonary valve had five cusps and one case in which the aortic valve was similarly anomalous.

Kissin (1936) reviewed 151 reported cases of quadricuspid pulmonary valve. He also reviewed three unreported examples of this condition, the specimens of which were in the McGill University Museum, and reported a case which he had observed. In his case Kissin judged that the malformation had been responsible for pulmonary valvular incompetence. Three of the reported cases also showed pulmonary regurgitation.

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Malformations of Semilunar Valves

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Bicuspid and Quadricuspid Semilunar Valves

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Congenital Malformations

E. Primary Endocardial Sclerosis

ENDOCARDIAL SCLEROSIS is the term applied to fibrous thickening of the mural endocardium. Two basic forms are to be recognized; secondary endocardial sclerosis and primary endocardial sclerosis. The secondary type is seen in a cardiac chamber or in chambers proximal to a valve that is atretic or severely stenotic In such locations endocardial thickening may be understood as a reaction to the dilatation of the involved chamber or chambers incident to the severe valvular malformation These changes have been discussed in the sections dealing with atresia of the valves

Valuable reviews on the relatively uncommon condition which has been designated variously as "primary endocardial sclerosis," "endomyocardial sclerosis" and "endocardial fibro-elastosis" have been presented by Gross (1941), Cosgrove and Kaump (1946) and Craig (1949). In this condition on gross inspection the involved mural endocardium is thickened, gray and glassy, and causes the prominences of the papillary muscles to be indistinct In some cases the endocardial thickening is restricted to the mural endocardium while in others there is associated thickening of one or more valves and the orifices of these valves may be stenotic. When the valves are involved it may be difficult or impossible to be certain of the classification It may be impossible to decide whether all of the endocardial changes had occurred simultaneously and so represent primary endocardial sclerosis or whether the valvular changes occurred first and the thickening of the mural endocardium is merely a secondary change.

The thickening of the endocardium is caused by heavy deposits of collagenous and elastic tissue fibers (Figures V-66*a*, V-66*b* and V-66*c*). Various authors have reported on microscopic changes in the myocardium. These include dilatation of the myocardial sinusoids, focal calcification (Figures V-66*d* and V-66*e*), and extension of the endocardial fibrous tissue into the subendocardial layers of the myocardium. Various other nonspecific changes, such as "cloudy swelling," vacuolization of the myocardial fibers and minor degrees of lymphocytic infiltration, have been described. Evidence of acute inflammation is not found. This condition affects almost exclusively the left side of the heart, particularly the ventricle. Right ventricular involvement is usually not present without left-sided involvement. When present, right ventricular endocardial sclerosis may be secondary to the effects of the primary changes in the left side of the heart.

When the valves are thickened they are composed for the greater part of loose, delicate myxomatous tissue which has been compared to embryonic tissue. Vascularization, fibrosis and cellular infiltration which might indicate an inflammatory basis are usually not encountered.

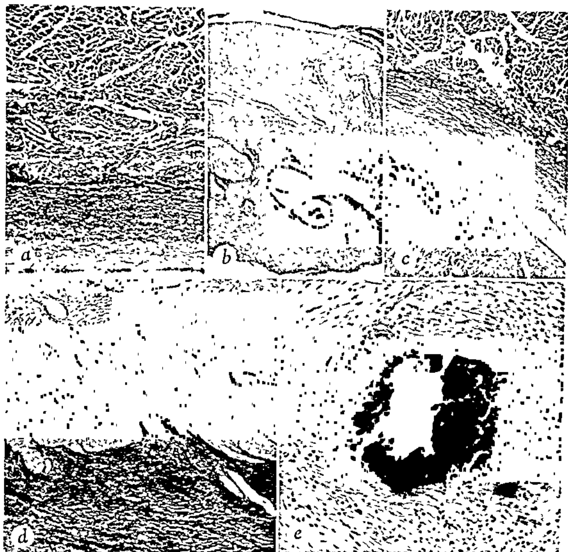


Figure V-66 The left ventricle in primary endocardial sclerosis *a-d* stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain

a Thickening of mural endocardium with elastic tissue and collagen X 60 From a case of dilated primary endocardial sclerosis, the heart of which is illustrated in Figure V-67 From a patient one and one-half years old

b Marked thickening of endocardium by collagen and elastic tissue which extend into the underlying muscle From a newborn infant with the contracted type of primary endocardial sclerosis See *d* and *e* for other illustrations in the same case X 11

c Focal mural thrombus showing thickened endocardium Other illustrations of this case in *a* and Figure V-67 X 45

d Beneath the thickened endocardium are prominent dilated myocardial sinusoids See *b* and *e* for other illustrations of this case

e Focal calcification in myocardium in a newborn infant with the contracted type of primary endocardial sclerosis (Illustrations *b*, *d* and *e* are taken from a case of the contracted type of endocardial sclerosis observed in the newborn by Drs Louise Wiegenstein, S W Lippincott and H D Chipps of Seattle, Washington. The sections and illustrations were prepared and the illustrations reproduced with their permission) Hematoxylin and eosin X 145



Figure V-67. Left ventricle in the dilated type of primary endocardial sclerosis From a female infant one and one-half years old Photomicrographs from this case appear in Figures 66*a* and *c*

Depending on the appearance of the left ventricle, primary endocardial sclerosis may be subdivided into the dilated type and the contracted type.

The Dilated Type of Endocardial Sclerosis

As the name implies, the left ventricular wall is dilated and usually is noticeably hypertrophied as well (Figure V-67). The *cardiac weight may be three to four times* normal for the age of the patient, the increase in weight being mainly on the basis of the left ventricular hypertrophy Focal thrombi in various stages of organization may be adherent to the dilated wall of the left ventricle (Figure V-67*c*). Some of the cases reported as examples of *congenital idiopathic hypertrophy* show the characteristic features of the dilated type of primary endocardial sclerosis (Kugel and Stoloff, 1933; Levine, 1934, Kugel, 1939; Cosgrove and Kaump, 1946) and should be so classified.

The large dilated left ventricle with endocardial thickening, which is commonly seen when the left coronary artery arises from the pulmonary trunk, is reminiscent of the appearance of the left ventricle in the dilated type of primary endocardial sclerosis When such an anomaly of the *coronary arterial system is found, as in one* of the cases of Craig, the condition should not be included under the classification of primary endocardial sclerosis but should be classified according to the vascular malformation.

Death in early infancy from cardiac failure is usual in either type of primary endocardial sclerosis. While the mechanism of failure in the dilated type is not clear, two factors are to be considered. One is nutritional in that the thickened endocardium evidently seals the left ventricular ostia of the thebesian veins and so may alter the dynamics of coronary blood flow. The other possible factor causing left ventricular failure may be mechanical interference by the endocardial fibrous tissue with left ventricular contraction and dilatation

Stadler and associates (1950) studied an infant born with complete heart block who died at the age of three and one-half months with endocardial sclerosis.

The Contracted Type (Constrictive Endocardial Sclerosis)

The heart in the contracted type of endocardial sclerosis has a strikingly different appearance from that in the dilated type. In the contracted type the left ventricle is small both in its absolute size and in relation to the size of the right ventricle. The right ventricle is dilated and greatly hypertrophied (Figures V-68*a* and V-68*b*). The disparity in size between the two ventricles makes the left appear as a mere appendage of the right. The left ventricular endocardium is diffusely thickened and may measure more than 1 mm. in thick-

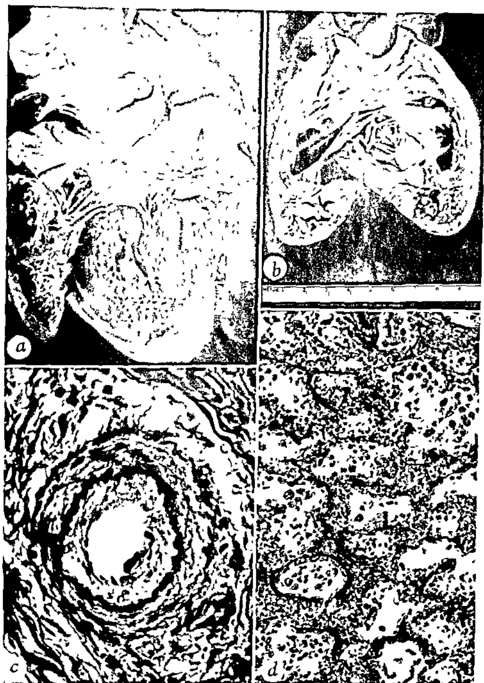


Figure V-68 The contracted type of primary endocardial sclerosis (constrictive endocardial sclerosis) in a boy five years of age who died of congestive cardiac failure

a The left side of the heart The endocardium of the left ventricle is thickened and trabeculated The left atrium is dilated The mitral valve is normal

b The right ventricle. Marked dilatation and hypertrophy This illustration is reduced to a greater extent than *a*

c. Small intrapulmonary artery showing medial hypertrophy and intimal fibrosis Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain X 340

d Lung The alveolar walls are thickened, mainly on the basis of capillary engorgement Prominent fibers of elastic tissue are in the alveolar walls Intra-alveolar hemosiderin-laden macrophages Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain X 140.

ness. It is pale gray and at times grossly resembles cartilage. The left atrium may be dilated and its endocardium may show a moderate degree of diffuse thickening. As in the dilated type, the valves may be normal or thickened.

The case of Gross, in which the patient was a newborn male infant, may be classified as belonging to the contracted type of primary endocardial sclerosis. In this case both the mitral and the aortic valves were thickened and stenotic. In addition the aortic valve was bicuspid. The sixth case of Cosgrove and Kaump was virtually identical in all respects. In the case of a boy aged five years which Dr. Howard B. Burchell and the author investigated, the heart had the gross characteristics of the contracted type of primary endocardial sclerosis. In it the cardiac valves were normal.

The functional alteration caused by the endocardial thickening in the contracted type is easier to understand than in the dilated type. Dr. Burchell has suggested that in this condition the thickened endocardium binds the muscle in a contracted state and prevents adequate diastolic excursion of the left ventricle. In this sense the thickened endocardium produces on the left ventricle a functional effect similar to that of an acquired constrictive pericarditis over this chamber. He has suggested the term *constrictive endocardial sclerosis* to convey in a simple and graphic manner both the anatomic and functional alteration in the contracted type of endocardial sclerosis. This seems to be an appropriate term.

If the endocardial sclerosis of the contracted type prevents adequate diastolic excursion of the left ventricle, there would be expected to exist a functional alteration similar to that in mitral stenosis; that is, interference with venous drainage of the lungs. The occurrence of right ventricular hypertrophy supports such a concept. Moreover, in the case of this condition which Dr. Burchell and the author studied, further evidence in support of this concept was furnished by the structural changes in the lungs. Microscopic examination of the lungs revealed changes identical with those seen in acquired mitral stenosis. There were medial hypertrophy and intimal fibrosis in the smaller intrapulmonary arteries and arterioles, capillary engorgement and thickening of the basement membranes of the alveolar walls and intra-alveolar collections of hemosiderin-laden macrophages (Figures V-68*c* and V-68*d*).

Developmental Basis

The critical reviews of Levine, of Gross and of Cosgrove and Kaump on the developmental basis of primary endocardial sclerosis have indicated that while early opinions favored inflammatory factors operating during fetal life, the evidence presented in the reported cases of this condition cannot be said to support such an assumption. At the present stage in our knowledge it is reasonable to deny an inflammatory basis, but another cause for the condition cannot be supplied. It may be assumed that whatever the cause, the conditon starts relatively late with respect to the period of cardiac development. Since characteristically there are no associated septal defects, it may be assumed that the endocardial changes occur after the heart is completely formed. Theoretically it may occur at any time after this stage is reached. Since the fully developed condition may be seen in the newborn, it is very likely that the thickening of the endocardium occurs relatively early in the period between the completion of the cardiac septa and birth. Why some cases of endocardial sclerosis are associated with a dilated left ventricle while others have a contracted left ventricle is unexplained.

Weinberg and Himelfarb (1943) reported on the occurrence of endocardial sclerosis of the dilated type in two siblings, one a girl who died at the age of four and one-half months, the other a boy, who was three and one-half months old at the time of death.

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Congenital Malformations

F. Malformations of Coronary Vessels

ANOMALOUS ORIGIN OF THE CORONARY ARTERIES

ANOMALOUS ORIGIN of the coronary arteries may be divided into two categories. In the first the coronary arterial supply is derived exclusively from the aorta but there is a variation from the normal pattern in the origin of the vessels. In the second group, one or both of the coronary arteries arise from the pulmonary trunk. The clinical features and functional characteristics of the two groups are profoundly different, and they will be discussed separately.

Anomalous Origin of Coronary Arteries from Aorta

Single Coronary Artery. The presence of a single coronary artery forms an interesting subject which has been reviewed by Krumbhaar and Ehrich (1938) and by Roberts and Loube (1947). According to *these authors, Hyrtl stipulated that the criteria* for true single coronary artery must include the finding that the entire heart is supplied by one coronary artery from which no conspicuous anomalous branches arise. Those cases in which the usual three coronary arteries are present but in which there is but one coronary ostium in the aorta are not to be considered as true examples of single coronary artery. While there are cases of the type of single coronary artery consistent with the postulate of Hyrtl, there are other types which have a single coronary ostium in the aorta. In discussing these matters, Krumbhaar and Ehrich stated that the classification of single coronary artery should include the latter types of cases as well as those which fulfill the postulate of Hyrtl.

The report of Roberts and Loube covers an analysis of 31 cases of single coronary artery, including nine cases of their own.

In addition to the type of single coronary artery acceptable to Hyrtl there are two other patterns. In one the single coronary artery gives rise to the right and left coronary arteries from which, in turn, the standard branches arise. In another there is a *dimple at the expected location of the* absent coronary artery, and a small twig lies in the expected location of the absent artery. Collateral connections are present between the single artery and the branches of the hypoplastic twig. The branches of this small vessel are larger than it is itself. Such a case is probably one in which the

two coronary arteries had formed normally but in which the ostium of one had become obliterated during fetal life Collateral connections between ramifications of the two arteries are responsible for blood flow to the branches of the "absent" vessel.

The latter type of pattern was observed seven times among the 31 cases analyzed by Roberts and Loube In five cases the left was the vessel without an aortic ostium. A case which is essentially similar was reported in 1948 by Reindell and Harnasch. In this case there was no left coronary ostium and no dimple at the expected origin of this in the aorta The right vessel was the single artery Its posterior descending branch swung around the lower margin of the heart and communicated with the anterior descending coronary artery. The latter vessel was narrower at the base of the heart than in the apical portion At the base, the anterior descending branch communicated with a narrow left coronary arterial stem which ended blindly as one proceeded proximally. The left circumflex coronary artery arose from the hypoplastic left coronary artery

Knop and Bennett (1944) reported on a single coronary artery arising from the right aortic sinus in a male infant aged five days In Figure V-69 is illustrated a hitherto unpublished case of single coronary artery which was observed by Dr. H B. Burchell in the Department of Pathology of the University of Toronto in 1934 Burchell's case was observed as an incidental finding in a male adult. In this case the single coronary artery arose from the right aortic sinus. Shortly after its origin it gave rise to a branch which entered the ventricular septum. This branch continued as a septal artery but also in turn gave rise to a branch which emerged in the location of the anterior descending coronary artery. The single coronary artery then ran in the right atrioventricular sulcus to reach the dorsal surface of the heart. After giving rise to the posterior descending coronary artery, the mother trunk continued into the left atrioventricular sulcus The terminal branches of this artery ended on the lateral aspect of the left ventricle

Of the 31 cases of Roberts and Loube seven had associated anomalies of the heart. In two of these there were bicuspid aortic valves, in a third a bicuspid aortic valve and atrial and ventricular septal defects, a fourth case had congenital stenosis of the mitral valve, two cases had the tetralogy of Fallot and the seventh case had complete transposition of the great vessels. Doubtless many more cases of single coronary artery are to be found in reports on various cardiac malformations but the single coronary artery without other cardiac malformations is a pathologic entity Its functional significance is usually negligible unless there is associated serious acquired occlusive disease. In these circumstances occlusion of the single artery would obviously be hazardous to the patient. With the report of a single coronary artery by White and Edwards (1948), the number of reported instances of adults with this entity was brought up to 28 Four of these had developed myocardial infarction which seemed a relatively high incidence of this complication

Origin of Left Circumflex Artery from Right Coronary. More common than single coronary artery, and perhaps the most common malformation of the coronary arteries, is the condition in which the left circumflex coronary artery arises from the right coronary artery The anomalous artery arises from the proximal part of the right artery and passes behind the aorta to reach the left atrioventricular sulcus It then follows the usual course of this vessel The artery arising from the left aortic sinus is the anterior descend' · coronary artery (Anatopol and K

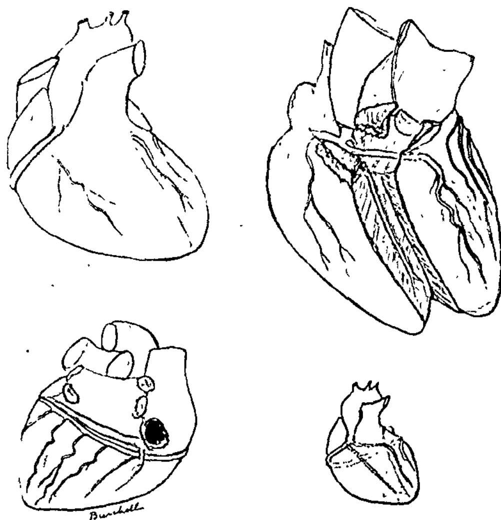


Figure V-69 Burchell's case of single coronary artery in an adult. (Illustrations prepared by *Dr H. B Burchell and reproduced with his permission*)

1933). In a study of 600 hearts from men, White and Edwards found this pattern in two cases.

At times the right and left coronary arteries may arise from the same sinus of the aorta, and in still other cases the left circumflex and the anterior descending coronary artery arise independently from the left aortic sinus, no left coronary artery, as such, being present.

Under rare circumstances part or all of the coronary arterial system branches from the innominate artery (Bland, White and Garland, 1933). In a case of Trevor (1912) the coronary arterial supply arose as a single branch from the innominate artery. The single coronary artery divided into two as it approached the heart. In this case there was also mitral atresia, a single ventricle and a persistent truncus arteriosus.

Anomalous Origin of One or Both Coronary Arteries from Pulmonary Trunk

Rarely both coronary arteries arise from the pulmonary trunk. With equal rarity the right coronary artery arises from this vessel while the left coronary artery arises normally from the aorta. Much more com-

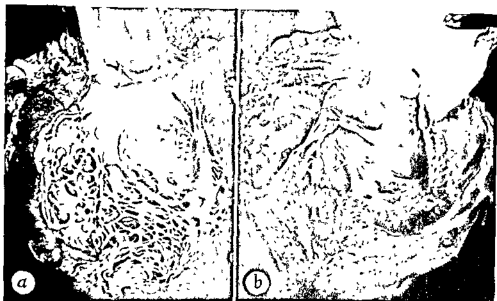


Figure V-70 Anomalous origin of the left coronary artery from the pulmonary trunk of an infant aged nine months (Specimen submitted by Dr Frederic Parker, Jr, Mallory Institute of Pathology)

a The left ventricle and aorta Only the right coronary artery arises from the aorta The left ventricle is hypertrophied and dilated, and its endocardium is greatly thickened

b The right ventricle and pulmonary trunk The left coronary artery arises from the left pulmonary sinus

mon than either of these two conditions, but rare in itself, is the condition in which the left coronary artery takes origin from the *pulmonary trunk* while the right coronary artery springs from the aorta

Origin of the Left Coronary Artery from the Pulmonary Trunk, with few exceptions, produces a well-defined pathologic and clinical entity (Bland, White and Garland, 1933) The infant usually appears normal at birth and for several weeks to months thereafter. This normal period is followed by attacks, often at the time of feeding, characterized by acute discomfort, short respiratory excursions and grunts; later there is sweating and apparent shock. It is believed that the attacks represent angina pectoris. The roentgenogram shows evidence of cardiac enlargement and the electrocardiogram reveals signs of hypoxia of the myocardium.

As stated in the comprehensive reviews of Soloff (1942) and Kaunitz (1947), those patients who suffer at an early period from the effects of the anomaly rarely live more than one year after birth. According to the analysis of Kaunitz, the oldest patient of those dying early was the one of Proescher and Baumann (1944), who died at the age of 13 months Eidlow and Mackenzie (1946) made the clinical diagnosis of anomalous origin of a coronary artery from the pulmonary trunk and later confirmed this diagnosis pathologically.

In patients with anomalous origin of the left coronary artery from the pulmonary trunk, who succumb during infancy, the pathologic feature is constant (Werlin and Dolgopol, 1939, Lyon *et al*, 1946, Gasul and Loeffler, 1949, Craig, 1949). The anomalous artery arises from the left pulmonary sinus (Figure V-70*a* and V-70*b*). There is considerable enlargement of the heart, particularly of the left ventricle which is dilated and hypertrophied. The changes are predominantly in the distribution of the left coronary artery. The endocardium of the dilated left ventricle

is thickened and gray, because of deposit of collagen and elastic tissue in this layer. Focal mural thrombi may also be found. The left ventricular myocardium may appear scarred on gross inspection. Microscopically, there are myocardial scars, evidently resulting from myocardial infarction. Bland, White and Garland have stated that the scarring tends to be concentrated toward the endocardial side of the myocardium of the left ventricle, a distribution comparable to the usual picture in a healed myocardial infarct resulting from acquired coronary arterial disease. In addition to scarring, the myocardium may show focal calcification sometimes recognizable as that of necrotic muscle. Occasionally, acutely infarcted muscle may be identified. At times wide, endothelium-lined, blood-containing sinusoids are present in the myocardium of the left ventricle. Atelectasis of the lungs may be caused by compression from the enlarged heart.

The incidence of anomalous origin of the left coronary artery from the pulmonary trunk is low. In the comprehensive review of Kaunitz, which included reference to the earlier review of Soloff, 27 cases were listed. These included two cases Kaunitz reported in which the patient was an infant. According to this author, in 20 of the 27 cases the patients were infants and in seven they were adults. This report did not include the two cases of Lyon and associates or the case of Eidlow and MacKenzie which appeared only shortly before the paper of Kaunitz. One of the patients of Lyon and associates was an infant female dying at six months of age, the other at three months. Werlin and Dolgopol's patient, dying at three months, is not mentioned in the several reviews.

In 1949 Gasul and Loeffler reported necropsies in three cases of anomalous origin of the left coronary artery from the pulmonary trunk. In a fourth case the clinical features seemed characteristic but permission for necropsy was not obtained.

For some unknown reason certain patients in whom the left coronary artery arises from the pulmonary trunk seem to show little or no effects of the malformation and live to adult life.

Kaunitz stated that seven instances of this malformation have been reported in adults who lived from 17 to 64 years. The oldest patient was evidently the one of Abbott. It may be mentioned parenthetically that Abbott (1927) stated that her patient was 60 years old. In some of the adults it has been explained that the anomalous artery functions not as an artery but as a vein, carrying venous blood from the heart to the pulmonary trunk while the right coronary is the only one which functions as a coronary artery.

Of 20 cases of anomalous origin of the coronary arteries from the pulmonary trunk, Soloff in 1942 found that in 16 the origin of the left artery arose anomalously and in two, *both coronary arteries arose from the pulmonary trunk*, while in the remaining two cases the origin of the *right coronary artery was anomalous*. According to this author Limbourg's patient, in whom the origin of both arteries was anomalous, lived 10 days. The other case with this malformation was that of Grayzel and Tennant, in which the patient died at the age of 10 days with tricuspid atresia, Type Ib. Reference to the latter case appears in the section on *Tricuspid Atresia*.

According to Soloff the two patients in whom the right coronary artery arose from the pulmonary trunk were adults at the time of death and these had evidently not suffered from any effects of the malformation.

Accessory Coronary Arteries Arising from the Pulmonary Trunk. These are occasionally encountered (Bland *et al.*).

In these cases the two standard coronary arteries arise from the aorta and the accessory artery is of incidental nature

A specimen from an adult patient with such an accessory coronary artery was submitted to me by Dr S E. Gould.

ANEURYSM OF THE CORONARY ARTERIES CORONARY ARTERIOVENOUS COMMUNICATIONS

In 1948 Scott reported an example of congenital coronary arterial aneurysm and made a review of the literature According to this author, including his case there were 47 recognized examples of localized aneurysm of one or both coronary arteries and five examples of diffuse aneurysms

As regards localized aneurysms, which are usually saccular, Scott stated that for some a congenital basis should be assumed This, he pointed out, was in contrast to the attitude of Packard and Wechsler (1929) who stated that the two chief causes for localized aneurysm of the coronary arteries were arteriosclerosis and infections, the latter chiefly of infected embolic character. Scott pointed out that in many of the so-called arteriosclerotic aneurysms there was minimal evidence of arteriosclerosis This author stated that of the 47 reported examples of localized aneurysm of the coronary arteries, 15 were to be considered as congenital in nature

Localized congenital aneurysm involves the left coronary artery more often than the right. Usually the aneurysm is single, although multiple aneurysms occur. While some patients with congenital coronary aneurysms may die as a result either of rupture of the aneurysm or of occlusion of the involved coronary artery, others live without any recognizable effects of the malformation

Scott found that of the 15 cases with localized coronary arterial aneurysms which were considered to be congenital, in 14 the patient was male and in only one was the patient female. The age of death of the 15 patients varied from five to 84 years, the average being about 47 years. The patient of Scott died at the age of 84 years from genito-urinary disease. In this patient there were two right coronary arteries One followed the usual course of the right coronary artery The other entered a large saccular aneurysm filled with laminated thrombi. This measured 10 cm. in greatest dimension. From this aneurysm the artery continued for a short distance to a second and smaller aneurysm. After a short course in which the artery had small aneurysmal dilatations it entered the pulmonary trunk, the mouth of communication being less than 2 mm. In addition to the aneurysms of one of the two right coronary arteries which have been mentioned, there were multiple small aneurysms of the other right and of the left coronary artery.

Scott stated that there were five examples of diffuse aneurysms of the coronary arteries in man reported since 1929 In four of the cases the right coronary artery and in one, the left coronary, was the site of the malformation. The diffuse aneurysms are characterized by tortuosity and dilatation of the involved artery over a distance of several centimeters.

In Harris' (1937) case there was a small communication between the dilated right coronary artery and the right atrium. The case of Halpert (1930) showed a communication between the dilated and tortuous right coronary artery and the coronary sinus. In the last two cases the patients were men, Harris' patient, aged 43 years, and Halpert's, aged 54 years Each of these two patients died of causes un-

related to the heart. In Emminger's case (1947), which was not quoted by Scott, the patient was a woman 43 years old at the time of death from uremia. In this case the right coronary artery was 1.4 cm. wide at its origin and widened progressively. At the posterior aspect of the heart the artery measured 2.0 cm in diameter In this region it communicated by means of a very tiny opening with the *vena magna cordis* The wall of the coronary sinus was thickened There were two ostia of the coronary sinus in the right atrium

In the case of Trevor (1912), in which the patient was a girl aged 11 years, there was a fusiform aneurysm of the right coronary artery. At necropsy there was a communication between the aneurysm and the chamber of the right ventricle as well as the lesions of bacterial endarteritis. Since the right coronary artery was wide along its entire course (the ostium was ½ inch or about 1.3 cm. in diameter), the aneurysm was considered congenital. The communication between the artery and the right ventricle was considered recent and a complication of bacterial endarteritis. A to-and-fro murmur had developed six days prior to the time of the patient's death

In an adult dog, Burchell (1939) found large endothelium-lined sinuses in the wall of the left ventricle. These seemed to have functioned as an arteriovenous fistula.

ANEURYSM OF THE AORTIC SINUSES CARDIO-AORTIC FISTULAS

Aneurysm of an aortic sinus usually involves the right aortic sinus The base of the aneurysm bulges toward the right ventricle or the right atrium. As a rule the two coronary arteries are also present. The conditions, in which the aneurysm is merely a blind pouch, are probably related developmentally to the conditions in which there is a communication between an aortic sinus on one hand and the right ventricle or the right atrium on the other. When communications occur they may be congenital in their entirety or the communications may represent secondary perforations of the base of a blind-pouched congenital aneurysm

In their report of anomalous channel between the aorta and the right ventricle, in which the patient was a newborn infant, Brown and Burnett (1949) stated that after consultation with Dr. B. M. Patten and Dr. A. Barry of the University of Michigan School of Medicine, they were of the opinion that the anomalous communication represented a developmental disturbance of the coronary blood vessels. They pointed out that coronary arteries develop as sprouts from the aorta which penetrate the myocardium. Here the arteries connect both with the coronary veins and with the intertrabecular spaces of the myocardium. Normally, the intertrabecular spaces become reduced in size

Brown and Burnett interpreted the anomalous communication in their patient as representing an accessory coronary artery which had retained connections with the intertrabecular spaces and that the latter had become enlarged and had also maintained connection with the chamber of the right ventricle. Aneurysm of an aortic sinus may be similarly explained, with the exception that the part of the communication removed from the aortic sinus becomes obliterated.

An extensive review of the subjects under consideration was made by Jones and Langley (1949) and much that follows is taken from their contribution. They designated aneurysms involving the aortic sinuses as either congenital or acquired. In their review they included 25 cases

believed to be examples of congenital aneurysm of the aortic sinus. Under this designation were considered aneurysms as well as communications between the aorta and one of the cardiac chambers.

Of the 25 cases, in 20 the right aortic sinus, and in five the posterior (noncoronary) sinus was involved. In no case was the left sinus involved. In four of the cases the lesions were represented as blind outpouchings of an aortic sinus while in 21 there was a cardio-aortic fistula. Of these 21 cardio-aortic fistulas five were considered congenital and 16 due to secondary rupture of a congenital aneurysm of an aortic sinus. Communications, either primary or secondary to rupture of an aneurysm, were usually located as follows. In those cases with involvement of the right aortic sinus the communication was with the right ventricle and in those involving the posterior aortic sinus the communication was with the right atrium. Rupture outside of the heart did not occur. Bacterial endarteritis was a rather common complication, being encountered in six aneurysms and leading to rupture in two instances. Another aneurysm that had ruptured subsequently became infected, nine months after the rupture. Infection did not occur in any of the five examples of congenital cardio-aortic fistulas.

Rupture is usually attended by dyspnea that sets in with dramatic suddenness and by a thrill and murmurs resembling those of patent ductus arteriosus. Death from cardiac failure may occur within a few days to several weeks or months after rupture.

The case of Maynard and Thompson (1948) (not cited by Jones and Langley) is a typical example of death shortly after rupture of an aneurysm of the posterior aortic sinus into the right atrium.

Cardiovascular anomalies which usually cause little disability are frequently associated with aneurysms of the aortic sinus and with cardio-aortic fistulas. Most common among these are variations in the structure of the aortic cusps. Ventricular septal defect, coarctation of the aorta, or stenosis of ostium infundibuli may also be associated.

ANOMALIES OF THE CORONARY SINUS

Dilatation of the Coronary Sinus is usually associated with a persistent left superior vena cava. This condition is of no functional consequence, since blood from the left innominate vein is carried to the right atrium by way of the connection of the persistent left superior vena cava with the coronary sinus.

Atresia of Right Atrial Ostium of the Coronary Sinus is an uncommon occurrence. In most of the cases there is a persistent left superior vena cava and also a communication between the two innominate veins (Grant, 1917; Harris, Gray and Whitney, 1927). In this way the venous blood of the heart flows in a retrograde manner in the coronary sinus and so into the left superior vena cava. From the left innominate vein the blood is carried to the right innominate vein and in this way by the right superior vena cava to the right atrium. Both Grant (1917) and Frontera (1950) observed similar anomalous arrangements in cats.

I have observed an unusual instance of this condition. There was no left superior vena cava. Blood from the coronary sinus was carried to the left atrium by way of a venous connection. An atrial septal defect was also present in this patient, a man aged 38 years who died of an intracranial tumor. Fieldstein and Pick (1942)

reported a case with similar venous abnormalities in an otherwise normal heart and reviewed five other reported examples.

The basis for atresia of the right atrial ostium of the coronary sinus is not explained, though the usual occurrence of a venous malformation in association is an indication that the condition is established during intra-uterine life. Grant stated that the right atrial ostium of the coronary sinus probably closes at a time after the transverse branch between the superior venae cavae has been established. According to Grant, Hutton suggested that the basic cause for the atresia might be a large thebesian valve. In the presence of elevated right atrial pressure the valve might be pressed into a closed position. With the connection between the superior venae cavae established, this causes no functional disturbance since the coronary blood would have an avenue of exit through the superior caval system. Secondary fusion of the enlarged thebesian valve with the wall of the right atrium might then follow.

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G. Malformations of the Aortic Arch System

DUCTUS ARTERIOSUS

THE DUCTUS ARTERIOSUS* is of clinical significance under one of three conditions: (1) when it is associated with other cardiovascular malformations; (2) when it takes part in the formation of a vascular ring which interferes with the function either of the trachea or of the esophagus; and (3) when, in the absence of other cardiovascular malformations, it remains patent.

The role of the patent ductus arteriosus as a collateral channel in isolated pulmonary atresia and isolated aortic atresia, in association with the tetralogy of Fallot, and the complexes formed when a patent ductus arteriosus is associated with coarctation of the aorta are discussed in the sections dealing with the associated malformations named. The vascular rings are

* The term "ductus Botalli" is frequently applied to the ductus arteriosus, but Gilchrist (1945) has pointed out that this is an incorrect designation According to Gilchrist, Franklin made a study of the historical aspects of the ductus arteriosus and determined that it was first described by Galen and that Botallo did not describe this structure.

considered in another section. Patency of the ductus arteriosus, in the absence of other malformations, is variously called *persistent patent ductus arteriosus*, *patent ductus arteriosus*, or *uncomplicated patent ductus arteriosus*.

Patent Ductus Arteriosus

Under this heading will be discussed the condition in which, in the absence of other malformations, the ductus arteriosus fails to undergo the normal process of anatomic closure after birth.

Morphologic Features of the Ductus. Normally the process which leads to anatomic closure of the ductus arteriosus starts in the fetus (Swensson, 1939, Jager and Wollenman, 1942). During the last trimester, fetuses show intimal ridges in the ductus, ridges which set the stage for eventual anatomic closure. At the time of birth and shortly thereafter, the media of the ductus shows microcysts of mucoid material and associated proliferation of the intimal and medial tissue. The thickening is usually eccentric and associated with breaks in the internal elastic lamina.

The ductus that remains abnormally patent shows a thin wall. It does not have the cordlike texture characteristic of the patent but closing ductus of the newborn. In adults the media of the patent ductus contains much collagen intermingled with the muscular tissue. The intima is thin (Figure V-71*a*). The picture is in striking contrast to the thick intima composed of laminated collagen and elastic tissue seen in the normally closed or closing ductus arteriosus.

The Time of Normal Anatomic Closure of the ductus arteriosus has been discussed in many reviews. Gibson (1900) stated that the ductal lumen usually is entirely obliterated within eight days, at the latest, from the time of birth. In contrast, Gilchrist (1945) stated that Alvarenga did not find a single example of perfect closure of the ductus arteriosus in 54 infants whose ages ranged up to one month. Gilchrist also stated that Christie found that in 65 per cent of infants two weeks old the ductus was still patent. Wells (1908) stated that in many normal infants the ductus arteriosus may remain patent up to three to six weeks after birth, although it usually closes earlier. My own experience has led me to believe that in most infants the ductus arteriosus as an effective channel is closed by the end of the second week after birth. At this time the ductal wall is thick and cordlike. Although it may be possible to pass a very narrow probe through the lumen at this time, the channel is usually so narrow as to be of no functional significance. Indeed, though the ductus arteriosus may be demonstrated at necropsy to be patent in the newborn infant, it may in fact have been functionally closed from the time of birth.

In their extensive studies on the function of the circulatory system of the fetus and newborn in the sheep, Barclay and associates (1939 and 1941) have demonstrated that the ductus arteriosus closes within four to eight minutes after birth. This closure is a functional one, but it is reasonable to postulate that it is maintained until the time that the ductus arteriosus is closed anatomically.

Crehan (1950) studied the arterial oxygen saturation of human infants by means of an oximeter placed on an ear as soon after birth as possible and at varying intervals during the first week after birth. He demonstrated that shortly after the umbilical cord was tied the arterial saturation levels assumed normal adult proportions, and remained in this state with the following exception: When the child slept, atelectasis probably resulted in the shunt of venous blood through the lungs, causing reduction in the oxygen saturation of the peripheral arterial blood. From the observations cited, it is evident that the fir

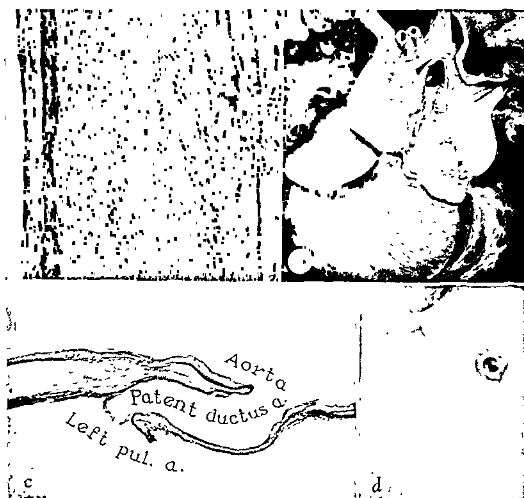


Figure V-71 *a* Aortic end of funnel type of patent ductus arteriosus from a woman aged 73 years The intima, which lies to the left, is very thin and is separated from the media by a layer of elastic tissue Other illustrations from this case appear in *c* and *d* Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 100

b Cylindrical type of patent ductus arteriosus in a female infant who died at nine months of age from cardiac failure. Another illustration of this case appears in Figure V-74c

c Funnel type of patent ductus arteriosus in a woman aged 73 years Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 2½.

d The pulmonary end of a patent ductus arteriosus The ductus protrudes into the lumen of the left pulmonary artery Other illustrations of this case appear in *a* and *c*.

ing of a patent ductus arteriosus in a necropsy on a newborn infant does not necessarily mean that anatomically demonstrated patency was associated with functional patency during life. It is conceivable that normally after birth the ductus remains closed by a state of spasm until such time as closure is effected by anatomic means.

Persistent patency of the ductus arteriosus, according to Patten, may be considered as an arrest in a fundamental process of growth The cause for this failure is not known, although there is an interesting and probably significant relationship between it and maternal rubella occurring during the first trimester of pregnancy (Swan, 1944; Swan *et al.*, 1946; Wesselhoeft, 1949). Campbell (1949) has emphasized that there is probably a variety of factors concerned in the appearance of patent ductus arteriosus as well as other congenital cardiac malformations.

The ductus that is not closed within two

months after birth probably is destined to remain patent in most cases Delayed closure during childhood seems possible but would be unusual (Gilchrist, 1945; Burchell, 1948).

In rare instances the ductus arteriosus is a *right-sided* structure, running between the right pulmonary artery and the aorta. Usually it runs between the left pulmonary artery and the aorta, inserting into the latter just beyond the origin of the left subclavian artery (Figure V-71*b* Often the ductus appears to originate from the bifurcation of the pulmonary trunk and this is frequently stated to be the case. Such a statement may be shown to be incorrect from a developmental point of view, and by careful anatomic study

Anatomic Types. Patent ductus arteriosus may be classified into (1) the cylindrical, (2) the funnel, and (3) the window types. The cylindrical type is the most common (Gilchrist, 1945); it possesses a relatively uniform caliber throughout its length, though the pulmonary end may be somewhat narrower than the aortic end The funnel type is characterized by a wide aortic ostium. The lumen of the ductus tapers toward the pulmonary end, and is considerably narrower at the pulmonary ostium than at the aortic end In some cases of the funnel type, in spite of the relatively narrow pulmonary ostium, the lumen is sufficiently wide to allow a shunt of significant magnitude. In other cases of the funnel type the pulmonary ostium is only from 1 to 3 mm. wide and the patency of the ductus is of no functional importance (Figure V-71*c*). In some of the latter cases there may be a bland thrombus in the pulmonary end of the ductus and the thrombus may protrude into the lumen of the left pulmonary artery The window type of patent ductus arteriosus is of considerable interest and is of importance to the surgeon. In this type the lumina of the aorta and the left pulmonary artery are simply in communication by way of an opening and there is no recognizable length to the ductus arteriosus The surgical problems in ligating such a ductus arteriosus are obvious. The window type of patent ductus arteriosus is usually found in relatively-older patients Although the window type of patent ductus arteriosus is the least common of the three types named, it is not rare.

In a study of the reports on cases of patent ductus arteriosus of persons 17 years of age or older, Keys and Shapiro (1943) found that this type was present in 17 per cent of 60 cases The author believes that the window type develops gradually. Evidently, as the pulmonary arterial system dilates because of the shunt, the pulmonary side of the ductus arteriosus is gradually effaced as it is incorporated into the gross structure of the left pulmonary artery

The window type of ductus arteriosus cannot be said to have length, but the cylindrical and funnel types have a length usually of less than 16 mm. and sometimes up to 20 mm. (Wells, 1908). The diameter of the ductus after death is frequently from 3 to 6 mm. Gilchrist stated that during life the patent ductus may be observed to be as wide as the aortic arch.

Potts and associates (1949) noted at operation a patent ductus the outside diameter of which was 18 mm Taylor and associates (1950) measured the patent ductus arteriosus at the time of operation. The outside diameter of the ductus varied from 7 5 to 13 mm, the average being 10 mm The approximate length of the ductus arteriosus varied from 6 to 10 mm., the average length being 8 mm. In all but one case the outside diameter of the ductus arteriosus exceeded the length. The pulmonary end of the patent ductus arteriosus often protrudes as a nipple (Figure V-71*d*) into the lumen of the left pulmonary artery

Functional Disturbances and Their Effects on Cardiovascular System. The direction of the flow of blood through the patent ductus arteriosus and the effects of this shunt on the heart and pulmonary vessels were appreciated by the early workers, but recent studies with cardiac catheterization and arterial puncture have furnished exact measurements of the magnitude of the shunt and have added exact information on the circulatory dynamics of this condition.

In 1885 White reported on a patent ductus arteriosus in the body of a man aged 52 years. When fluid was injected into the peripheral arteries of this subject, some of it entered the pulmonary arteries through the ductus arteriosus.

Gibson (1900), appreciating the course of the blood through the patent ductus arteriosus, was able to state that this condition gave a characteristic murmur and thrill. Realizing the effects of the abnormal communication, Munro in 1907 suggested that attempts be made to close it surgically. The first successful surgical closure (Gross and Hubbard, 1939) was performed 31 years later.

Before birth the blood flows through the ductus arteriosus from the pulmonary arterial system into the aorta, because the resistance to pulmonary flow equals or exceeds the resistance to systemic blood flow. After birth a gradual gradient of pressure appears to develop between the pulmonary and systemic arterial pressures In the newborn infant with a persistent patent ductus arteriosus the flow through the ductus arteriosus is probably minimal but grows in volume as the pressures in the two systems deviate from each other. This may account for the fact that in infants and young children the characteristic murmur of a patent ductus arteriosus may not be present (Burchell, 1948). It is not known when the shunt through the persistent patent ductus arteriosus assumes its full capacity, but the shunt is from the aorta into the pulmonary arterial system (Figure V-72).

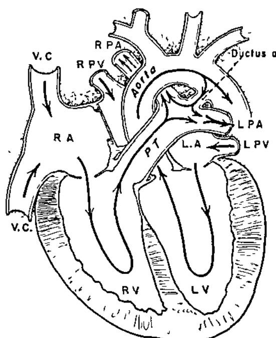


Figure V-72 The circulation in a patent ductus arteriosus

The *amount of blood* which passes through this abnormal channel may reach surprisingly large proportions.

Eppinger, Burwell and Gross (1941) demonstrated that when the thorax was open in preparation for surgical closure of a patent ductus arteriosus the amount of blood that was shunted through the ductus arteriosus per minute might vary from 3 9 liters in one patient to 19.5 liters in another. These figures are comparable to those obtained with the thoracic cavity closed, the studies being done by means of cardiac catheterization. Taylor and associates (1950) observed that in six patients with a patent ductus arteriosus the average flow through the ductus arteriosus was 7.4 liters of blood per minute. The ranges were 1.6 to 17.7 liters. These investigators found in 12 patients that the flow through the ductus varied from 23 to 80 per cent of the left ventricular output and averaged

44 per cent. They could find no consistent correlation between the volume of flow through the ductus arteriosus and the difference between the pulmonary and systemic arterial pressures. Likewise there was no correlation between the outside diameter of the ductus arteriosus and the volume of the shunt. However, there was a tendency for the volume of the shunt on one hand to be correlated with the diameter of the ductus arteriosus, and the pressure differences between the systemic and the pulmonary arterial pressures, taken together, on the other

The physiologic studies on patients with patent ductus arteriosus have demonstrated the remarkable capability of the lungs in most patients to receive great quantities of blood without significant elevations of pulmonary arterial pressure (Dexter *et al*, 1947, Cournand, 1947, Dexter, 1948).

Taylor and associates found in five patients with patent ductus arteriosus that the average pulmonary arterial systolic pressure was 30 mm. of mercury and the average diastolic pressure, 17 mm. of mercury. These figures were considered to be within the upper limits of normal In the same study there was a sixth patient who exhibited pulmonary hypertension In this patient the pulmonary arterial systolic pressure was 108 mm. of mercury and the diastolic pressure, 29 mm. of mercury. In yet another patient with patent ductus arteriosus studied at the Mayo Clinic there was pulmonary hypertension The patient was a boy aged 10 years in whom the pulmonary arterial systolic pressure was 108 to 113 mm. of mercury and the diastolic pressure, 59 to 64 This case was discussed by Burchell (1948) and later reported in greater detail by DuShane and Montgomery (1948). Dexter and associates (1947) found pulmonary hypertension in a woman aged 26 years with a patent ductus arteriosus. In this patient the pulmonary arterial systolic pressure was 63 mm of mercury and the diastolic 35. Cournand (1947) and Cournand and associates (1949) reported on the presence of pulmonary hypertension in two patients, each aged three years, with patent ductus arteriosus These isolated cases with pulmonary hypertension and patent ductus arteriosus are mentioned to emphasize the fact that this combination of conditions is unusual. The pulmonary hypertension is to be considered a complication of patent ductus arteriosus. It will be discussed further in this section under Complications of Patent Ductus Arteriosus



Figure V-73 Roentgenogram of the thorax in a boy aged 11 years with patent ductus arteriosus There is characteristic prominence of the shadow of the conus arteriosus and congestion of the lungs.

In the uncomplicated cases of patent ductus arteriosus the shunt causes secondary changes in the heart and in the pulmonary vessels. Demonstration of these secondary changes is an aid in the clinical diagnosis of patent ductus arteriosus (Eppinger and Burwell, 1940, Nichol and Brannan, 1947).

In the first place the pulmonary arterial system, receiving abnormally great volumes of blood, becomes dilated. This feature is recognized roentgenographically by prominence of the conus arteriosus an

by evidence of pulmonary congestion (Figure V-73). The dilated pulmonary arterial system may interfere with the function of the left recurrent laryngeal nerve and cause hoarseness (Thompson and Kistin, 1948).

The blood which flows through the ductus arteriosus has a traumatizing effect on the wall of the left pulmonary artery opposite the pulmonary ostium of the ductus This results in a localized patch in which the intima is thickened by fibrous tissue, partly collagenous and partly elastic (Figure V-74*a*) This lesion has long been recognized. On the basis of the suggestion made by Dr. Howard B. Burchell, my associates and I have called this patch a "jet lesion." Such lesions are also seen in experimental animals in which an artificial ductus arteriosus has been established (Leeds, 1948; Ross and Murphy, 1949). These lesions are not atheromatous and should not be so designated or confused with the foci of true atheromas which may e scattered in the greater pulmonary arteries

Since the shunted blood is carried to the left side of the heart, the pulmonary veins and left atrium and the left ventricle are dilated (Figure V-74*b*) It may be a matter of importance that the mitral valve is dilated less than either of the two left-sided chambers. Thus if the left side of the heart is viewed as a unit, it may be said to have an hour-glass shape, the mitral valve representing the constricted portion of the hour-glass (Figure V-74*c*).

The wall of the left ventricle and particularly that of the left atrium often shows secondary endocardial sclerosis. This is probably a reaction incident to dilatation of the chambers Left ventricular hypertrophy is commonly present and may be associated with right ventricular hypertrophy. At other times the left ventricle is not materially hypertrophied and the right ventricular wall is thickened. Still other cases show little hypertrophy of either ventricle.

In a study of 16 adult patients in whom necropsy at the Mayo Clinic demonstrated a patent ductus arteriosus, Douglas (1948) found hypertrophy of the right ventricle in three cases, of the left ventricle in six cases, and no significant hypertrophy of either ventricle in the remaining seven cases. There was a fairly close correlation between cardiac failure and ventricular hypertrophy. In addition there was some tendency for right ventricular hypertrophy to be associated with occlusive vascular changes in the lungs. In the 16 adult patients studied by Douglas the cardiac weight varied from 195 to 895 grams, the average being about 475 grams.

Complications and Survival. Comprehensive reviews of the literature pertaining to complications of patent ductus arteriosus are to be found in the works of Bullock, Jones and Dolley (1939) and of Keys and Shapiro (1943).

Bullock and associates limited their study to patients who were three years of age or older at the time of death and in whom necropsy proved that no significant anomaly was associated with the patent ductus. They studied 80 such cases, 76 of which were taken from the literature and four from the files of the Los Angeles County Hospital. By the age of 14 years, 11 patients (14 per cent of the group) had died of their malformation. By the age of 30 years one-half of the patients had died as a result of the patent ductus arteriosus, and by the age of 40 years 71 per cent of the patients had died. Two of the patients in this study lived to the age of 66 years.

Bullock and associates found that the two leading causes of death were *congestive cardiac failure* and *bacterial endarteritis.* Forty-two (53 per cent) of the 80 patients died of the bacterial complication, while 18 (23 per cent) died of



Figure V-74 *a* Left pulmonary artery in a case of patent ductus arteriosus in which ligation of the ductus had been performed four and one-half years before death The intima is greatly thickened in part by elastic tissue The concentration of elastic tissue appearing in the upper part of the figure is separated from the media by a layer of collagen Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 125 (From Dry, Harrington and Edwards, 1948)

b The pulmonary veins and the left side of the heart in a man aged 24 years with patent ductus arteriosus The pulmonary veins are dilated There is endocardial thickening of the dilated left atrium and dilated and hypertrophied left ventricle

c The left atrium and left ventricle in a case of patent ductus arteriosus from an infant who died at nine months of age from cardiac failure The dilatation of the left ventricle and left atrium in association with a relatively nor
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congestive cardiac failure. Five patients (six per cent) were listed as dying either of rupture of the ductus or of left ventricular failure. In four patients death seemed to have been caused by a combination of the effects of the patent ductus arteriosus and of some other condition Bullock and associates thought that 69 (86 per cent) of the 80 patients died as a result of the patent ductus arteriosus.

Keys and Shapiro studied 60 cases of patent ductus arteriosus in which the patients were 17 years of age or older at the time of death. Some of their cases were also analyzed in the report of Bullock and associates Fourteen male patients and 46 female patients were represented. The average age of death among the male patients was 38 9 years and among the female, 35.5 years. The oldest man was 58 years and the oldest woman 66 years. These authors estimated that a patent ductus arteriosus caused a reduction in life expectancy of 23 years in men and of 28 years in women. Approximately four out of five patients died as a result of the malformation The leading cause of death was bacterial endarteritis, which accounted for death in 40 per cent of the 60 patients studied. Congestive cardiac failure accounted for death in nearly 30 per cent of the patients. Though this complication is unusual in infancy or early childhood it does occur (Hueter, 1900)

The study of Gelfman and Levine (1942) of 181 patients with congenital cardiovascular malformations, who were two years of age or older, included 14 patients with patent ductus arteriosus Two of these had associated the tetralogy of Fallot, one, coarctation of the aorta, and one, bicuspid semilunar valves. Of the 10 subjects in whom the patent ductus arteriosus was the sole malformation, two had a superimposed infectious process. One-half of their patients with patent ductus arteriosus died during the second and third decades of life. The oldest patient was 65 years.

Abbott (1925) observed that there were 67 examples of patent ductus arteriosus among 555 cases with clinically significant malformations. Fifteen of the patients with patent ductus arteriosus had bacterial endarteritis.

In 10 of the 60 cases of patent ductus arteriosus analyzed by Keys and Shapiro there was a pulmonary arterial aneurysm and in two of these, as in the case of Durno and Brown (1908), rupture of the aneurysm caused death.

Rupture of a patent ductus arteriosus, in the absence of an aneurysm, is uncommon Bronson and Sutherland (1918) quoted a case of Roeder in which the patient, a female infant aged three days, died of rupture of a dissecting aneurysm of the ductus arteriosus. In another case of Roeder, in which the patient was a male infant aged two days, a fusiform aneurysm of the ductus arteriosus ruptured.

A bland thrombus of the ductus is uncommon, when present it is usually found in the newborn period (Jager, 1940). According to Wells (1908), Rauchfuss observed thrombosis 12 times in 1400 necropsies on infants. It is of passing interest to note that the occurrence of this complication was used by the earlier workers in incorrectly explaining that normal closure of the ductus arteriosus was accomplished by a process of organization of a ductal thrombus. In the newborn period, thrombosis of the ductus arteriosus is usually an incidental finding (Figure V-75*a*). Pinniger (1949) reported on the occurrence of a fusiform aneurysm of the ductus arteriosus containing an infected thrombus in an infant aged 18 days who had had a staphylococcal abscess of the arm. The necropsy also showed pulmonary abscesses. Jager's case was unusual in that his patient, a woman aged 55 years, had a bland thrombus in a patent ductus arterio-

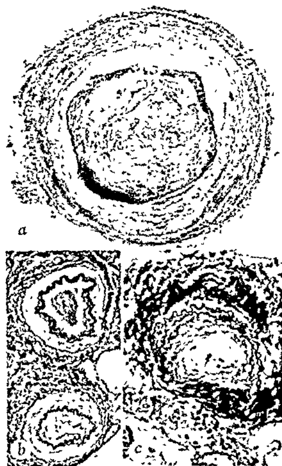


Figure V-75 *a* Thrombosis of a patent ductus arteriosus in a male infant 11 days old Hematoxylin and eosin X 11

. . from a woman

a

a

thickening ... elastic tissue stain, counterstained with van Gieson's connective tissue stain X 80

- Pulmonary arteriole in a woman aged 23 years ... luminal ... is frag- ... tic tissue stain, counterstained with van Gieson's connective tissue stain X 275.

sus Death was caused by embolism to the superior mesenteric artery with resulting intestinal infarction

Although there is clinical evidence that cardiac enlargement may recede after ligation of a patent ductus arteriosus (Gross, 1947), the enlarged left ventricle may constitute a hazard to the patient In a case which was reported by Dry and associates (1948), sudden death occurred about four and one-half years after a patent ductus had been ligated. The heart was greatly enlarged. The left ventricle particularly was hypertrophied and dilated. It seemed that in this case the operation was followed by little reduction in the size of the heart and that the enlarged heart had failed, causing death.

Bacterial endarteritis in patent ductus is uncommon during the first decade (Gilchrist). Schlaepfer (1926) reviewed 19 cases of patent ductus arteriosus complicated by bacterial endarteritis Between the ages of one and 10 years there was one case, between 11 and 20 years, four cases; between 21 and 30 years, nine cases, and between the ages of 31 and 40 years, four cases. One patient was 45 years of age. This group comprised six male and 13 female patients. The infection may originate either in the pulmonary end of the ductus or in the wall of the left pulmonary artery opposite the pulmonary ostium of the ductus The infection probably starts at areas subjected to trauma. The traumatic effect of blood striking the left pulmonary artery is evident. It is understandable that the ductus itself should be traumatized since the pulmonary end of this struc' is often narrower than the aortic (Wells, 1922) In 11 of the 19 cases viewed by Schlaepfer only the pulm orifice of the ductus arteriosus co thrombi while in three cases thro' truded from both ostia of the ductu

From the ductus the infectio spread to the pulmonary arterial as in the case of Graybiel, St' Boyer (1938), which was the f which surgical closure of a p' arteriosus was attempted. In Hines and Wood (1935) spread to involve the pulmona the pulmonary valve. Pulm are common as a result of Emboli also occur in the sy

but are less frequent. In Schlaepfer's 19 cases splenic infarcts were encountered in nine cases and renal infarcts in seven.

In fatal cases involvement of the aortic and mitral valves by bacterial endocarditis is common Jager, who reviewed 35 fatal cases of septic thrombosis of a patent ductus, stated that in only five of the cases were the valves uninvolved The tricuspid valve is least commonly affected. Involvement of the aortic and mitral valves probably results from seeding of the pulmonary blood with bacteria which are carried by the pulmonary veins to the left side of the heart Whereas results from ligation of an infected ductus arteriosus are usually good, one important barrier to recovery is the secondary involvement of the cardiac valves (Touroff and Vesell, 1940; Touroff, 1943) Since the infecting organism is usually a *Streptococcus viridans,* which is sensitive to penicillin, it is reasonable to expect that secondary valvular involvement will be less serious than it was in the early days of ligation of the ductus for infected patent ductus arteriosus.

Aneurysm of the pulmonary arteries was the subject of studies by D'Aunoy and von Haam (1934), Boyd and McGavack (1939), and Deterling and Clagett (1947) The aneurysm may result from acquired disease, such as syphilis. Congenital malformations of the heart of types associated either with an arteriovenous shunt or with pulmonary hypertension also represent important underlying factors in causing pulmonary arterial aneurysms. The most common malformation is patent ductus arteriosus. In the cases reviewed by Boyd and McGavack and by Deterling and Clagett patent ductus arteriosus occurred in about one-fifth of the subjects with pulmonary aneurysm This malformation was more common than all others combined as a basis for pulmonary arterial aneurysm. The aneurysm may be either saccular or fusiform. It involves the pulmonary trunk more commonly than either of the major pulmonary arteries. Usually there is bland destruction of the arterial wall leading to formation of aneurysm. Occasionally the aneurysm is mycotic and represents a complication of bacterial endarteritis, as in the second case of D'Aunoy and von Haam. These authors called attention to the opinion of Krzyszkowski that the aneurysm may result from the destructive effect of the shunted blood striking the pulmonary arterial wall opposite the patent ductus arteriosus. Though this may be the basis for some of the aneurysms, it does not seem to be a consistent cause for the nonmycotic pulmonary aneurysms in cases of patent ductus arteriosus.

The development of *pulmonary hypertension* in the patient with a patent ductus arteriosus represents an unusual complication, but one which introduces a number of interesting clinical, morphologic, functional and surgical problems. Clinically, significant pulmonary hypertension results in signs quite different from those in the uncomplicated case of patent ductus arteriosus (Burchell, 1948). The characteristic continuous murmur and thrill may be lost The electrocardiogram may show right axis deviation, a feature not seen in the uncomplicated condition The oxygen saturation of the femoral arterial blood may become subnormal

Several factors, some of which operate together, may be responsible for pulmonary hypertension in cases of patent ductus arteriosus. Some of these follow: (1) Occlusive changes may occur in the smaller pulmonary arteries and arterioles; (2) the capacity of the pulmonary vascular tree to accommodate an extra amount of blood may be exceeded; (3) while the left atrium and left ventricle dilate sufficiently to accommodate the great volumes of blood carried to them, the mitral valve may dilate but little and produce a zone of relative stenosis (Cournand *et al.*, 1949); (4) fail-

ure of the left ventricle may be responsible for impaired venous return from the lungs and elevation of the pulmonary pressure. In patients with pulmonary blood pressures within the upper limits of normal, Taylor and associates (1950) demonstrated that ligation of the ductus results in a prompt fall in the pulmonary arterial blood pressure. Such a response indicates that the latter three factors, whether operating separately or together, must play some role in causing increased resistance to pulmonary flow and associated elevated pressures. In some instances dramatic morphologic changes in the intrapulmonary vessels seem to be important factors in causing increased resistance to pulmonary flow and pulmonary hypertension.

Cases with occlusive pulmonary vascular lesions have been described by Bettinger (1941), Keys and Shapiro (1943), Chapman and Robbins (1944), Douglas and associates (1947), and Ulrich (1947)

Organic changes present in the pulmonary vessels may be focal and are predominantly those of intimal fibrous proliferation associated with luminal narrowing The vessels chiefly involved are the small arteries and the arterioles (Figure V-75*b* and V-75*c*) The intimal changes are not to be considered atheromatous They may result from trauma of excessive pulmonary blood flow by itself, or that associated with unusual vibrations of the vascular tree. Medial hypertrophy usually does not occur in significant degree. It is to be emphasized that while organic changes of widespread nature may be present in the intrapulmonary vessels in patent ductus arteriosus, this phenomenon is unusual.

Welch and Kinney (1948) reviewed 25 cases of patent ductus arteriosus and found only one in which the changes in the intrapulmonary vessels exceeded in degree those in their control cases. This case had been reported by Chapman and Robbins. Douglas (1948) measured the intrapulmonary arteries in 16 fatal cases of adults with patent ductus arteriosus and found reduction in diameter of the pulmonary arteriolar lumina in 10 cases.

Severe occlusive pulmonary arteriolar changes in a subject with patent ductus may cause elevated pulmonary pressure and a concomitant reduction in the gradient of pressure between the aorta and pulmonary arteries. Such a change would tend to reduce the volume of the shunt, and at times the pulmonary pressures may exceed systemic arterial pressures and cause pulmonary arterial blood to flow through the ductus arteriosus into the aorta. Such a phenomenon would explain the finding of reduced hemoglobin in the femoral arterial blood. While the organic vascular changes may be reasonable for a decreased shunt and consequently a decreased load on the left side of the heart, they concomitantly put a greater load on the right ventricle and favor the development of right ventricular hypertrophy While the right ventricle can, under such circumstances, assume the function of a systemic ventricle, its failure is inevitable.

When ligation of the ductus arteriosus is contemplated in the presence of pulmonary hypertension, it is difficult to predict whether ligation will cause a reduction in pulmonary blood pressure. From the relatively small amount of evidence so far available, it is known that ligation of the patent ductus arteriosus in the presence of pulmonary hypertension may be followed by some reduction in the hypertension (Cournand *et al*, Taylor *et al*). This reduction may be in part immediate and in part delayed The immediate reduction may be explained by a combination of factors If one assumes in such a case that organic vascular changes exist, it may be considered that the vascular changes had reduced the adaptive capability of the lungs to receive great volumes of blood. With the reduction in amount o

pulmonary blood flow incident to elimination of the shunt, a stable situation might be reached. While the pulmonary capacities for great volumes of blood had been impaired, the new and reduced volumes of circulating blood might be within the existing capabilities of the pulmonary vascular tree to accommodate blood without greatly increased pressure. Reduction in the volume of pulmonary blood flow might allow recovery of a failing left ventricle. The reduced volume of blood entering the left side of the heart might be better accommodated by the mitral valve These factors may influence reduction in pulmonary blood pressure after ligation of a patent ductus arteriosus

It is appreciated that patients with severe and widespread occlusive pulmonary vascular changes might show little if any reduction in pulmonary blood pressure after ligation of the ductus arteriosus.

Aneurysm of the Ductus Arteriosus

Aneurysm of the ductus arteriosus is a rare condition and one that usually causes no functional disturbances The usual picture is like that illustrated in Figure V-76 The pulmonary end of the ductus is closed while the aortic end is patent and dilated to aneurysmal proportions Superficially such a lesion may appear to be an aortic aneurysm (Altschule, 1937). Histologically the wall of the aneurysm is composed of ductal rather than aortic tissue. Since a thrombus may form in the aneurysm, peripheral arterial embolism is a potential complication. Graham (1940) reported two unusual cases of aneurysm of the ductus arteriosus. Each aneurysm was exceptionally large and gave the clinical impression of a mediastinal neoplasm.

The occurrence of thrombosis of fusiform aneurysms of patent ductus arteriosus has been discussed under complications of patent ductus arteriosus.

Absence of the Ductus Arteriosus
Right-sided Ductus Arteriosus
Double Ductus Arteriosus

Absence of the ductus arteriosus is seen in conjunction with certain malformations of the heart. These defects have one feature in common: The two circulations mix either in a common ventricle or in a persistent truncus arteriosus, or the pulmonary artery communicates with the aorta. The reason for the absence of the ductus arteriosus under these circumstances is readily understandable when one reflects on the fate of that part of the right sixth aortic arch beyond the point of origin of the right pulmonary artery under normal conditions. This portion of the right sixth aortic arch is the right ductus arteriosus. Under normal circumstances in the embryo the blood which leaves the heart is directed toward the left. This is accompanied by retention of the left-sided ductus and a gradual diminution in size of the right ductus. The atrophy of the latter be-



Figure V-76. Aneurysm of the ductus arteriosus in a man aged 67 years The pulmonary end of the ductus arteriosus is closed, while the aortic end is patent and dilated to aneurysmal proportions. A thrombus is contained in the aneurysm. An. indicates aneurysm, *Lig. A*, pulmonary end of closed ductus arteriosus, *L P A*, left pulmonary artery.

comes so complete that by the time the fetus reaches maturity there is normally no vestige of a right-sided ductus arteriosus.

In the normal fetus the left-sided ductus acts as an overflow valve, so to speak. Of the blood which leaves the right ventricle only a portion is received by the pulmonary arteries. The remainder flows through the ductus into the descending aorta. In such conditions as cor triloculare biatriatum, persistent truncus arteriosus, the tetralogy of Fallot and the Eisenmenger complex, other "overflow valvular" mechanisms exist, depending on the malformation. In each the aorta is already in communication either with the single ventricle or with both ventricles. Under any of these conditions the amount of blood which flows through the ductus during fetal life may be minimal, and so the ductus may disappear not only on the right side as in the normal subject, but also at times on the left side.

Claims of absence of the ductus arteriosus in patients with normally developed cardiovascular systems should be considered skeptically since it is unlikely that such a condition would allow a fetus to attain normal development From a review of the fetal circulation (Chapter II), it is evident that in the fetus with normally formed ventricular and truncoconal septa the ductus arteriosus is an important overflow channel for blood leaving the right ventricle. It must be admitted that a fetus could survive with absence of the ductus and with intact ventricular and truncoconal septa. This would require the shunting of a considerable amount of blood through the foramen ovale into the left side of the heart Ordinarily the report of absence of the ductus in the presence of an otherwise normally formed cardiovascular system means that the ductus had been overlooked. This error may result from the presence of an unusually delicate left ligamentum arteriosum or failure to find an existing right-sided ductus arteriosus.

In the tetralogy of Fallot with a right aortic arch, the ductus may be a left-sided structure and insert into the left innominate or the left subclavian artery instead of into the aorta Such an arrangement in the fetus does not allow the ductus to function normally, since the systemic connection of the ductus is not with the descending aorta. Any blood passing through the ductus would find its way either to the head or to the left upper extremity. This, however, should not cause embarrassment to the fetal circulation since in the tetralogy of Fallot the aorta is in communication with the right ventricle. Therefore, there is an adequate and direct channel for right ventricular blood to the aorta and so to the placenta.

The subjects of *right ductus arteriosus* and *double ductus arteriosus* will be discussed under those malformations of the aortic arch system which are concerned with formation of vascular rings

COARCTATION OF THE AORTA

Classification. Coarctation of the aorta is a condition in which the aortic lumen either in the arch or just beyond is significantly narrowed on a congenital basis It is a relatively uncommon condition. Goodson (1937) encountered, in more than 77,000 necropsies taken from several reports, 55 examples of aortic coarctation.

The classification commonly used, that of Bonnet (1903), distinguishes the infantile and the adult types of coarctation. In the infantile type the coarctation lies

proximal to the ductus arteriosus and usually distal to the left subclavian artery. The adult type includes those cases in which the narrow zone lies either at the level of the aortic insertion of the ductus or immediately distal to it In the infantile type the ductus is usually patent; in the adult type it is usually closed.

The classification of Bonnet is not adequate It does not reserve a place for those cases in which the coarctation lies in an uncommon position, between the origin of the left common carotid artery and that of the left subclavian artery. Furthermore, it does not include those cases in which, in the same individual, there is coarctation of the aorta in the vicinity of the insertion of the ductus arteriosus and stricture of the right subclavian artery at its origin Regardless of these deficiencies in the Bonnet classification, determination of the exact location of the coarctation is not as important as is the consideration the closure or patency of the ductus rteriosus. The reason for emphasis on the latter consideration is that when the ductus arteriosus is closed, the intrapulmonary arteries show relatively little change. Those cases in which the ductus is open show significant morphologic changes in the intrapulmonary arterial vessels.

The following classification, though somewhat lengthy, seems adequate

1. Coarctation of the aorta with closed ductus arteriosus
   - (a) Coarctation in vicinity of the ligamentum arteriosum
   - (b) Coarctation in unusual locations
   - (c) Coarctation associated with stenosis of the right or the left subclavian artery
2. Coarctation of the aorta with patent ductus arteriosus
   - (a) Coarctation distal to the aortic mouth of the ductus
   - (b) Coarctation proximal to the aortic mouth of the ductus
     - (1) Without systemic collaterals
     - (2) With systemic collaterals

Coarctation of Aorta with Closed Ductus Arteriosus

Pathologic Anatomy of Aorta and Heart. The usual location of coarctation of the aorta is opposite the aortic insertion of the ligamentum arteriosum. As a rule it occurs either at or just distal to that point but may occur somewhat proximal to it.

Externally, the aorta tends to have a constant appearance. Corresponding to the zone of luminal narrowing, there is a concavity of the outer contour of the vessel. This involves the cephalic, ventral and dorsal aspects. Thus, the external concavity involves all walls except the caudal, into which the ligamentum arteriosum inserts. The caudal wall may be regular or distorted convexly (Figure V-77*a* and V-77*b*)

While the zone of greatest narrowing is frequently short and clearly defined, the diameter of the aorta tapers gradually as the stricture is approached. At times, however, there may be a zone of narrowing for a distance of 1 cm or more Proceeding distally from the coarctation, the aorta dilates gradually. The configuration in the region of the coarctation may be said to resemble two cones, the apices of which have been placed end to end.

When the interior of the aorta is examined, it becomes immediately apparent that the lumen at the involved zone is considerably narrower than might be indicated from the external diameter. At this level a diaphragmatic structure, containing a tiny perforation, lies across the lumen of the aorta. The small opening constitutes the aortic lumen at the involved level. The

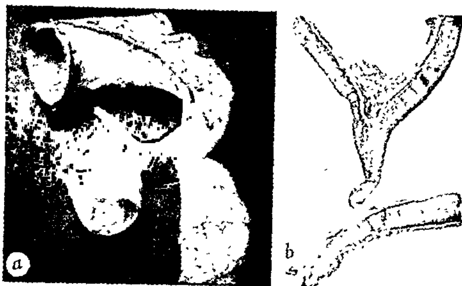


Figure V-77 *a* Coarctation of the aorta beyond the ligamentum arteriosum The superior surface of the aorta shows characteristic deformity From a man 51 years of age

b Photomicrograph of a segment of the aorta removed surgically because of coarctation by Dr O T. Clagett The aorta is sectioned longitudinally. The proximal portion is to the right, the distal to the left While the inferior wall is regular in outline, the superior wall shows characteristic infolding of the media producing an eccentric lumen of microscopic size From a woman 30 years old Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 4

narrowed lumen lies toward the lower side of the aorta

In a consideration of the size of the lumen at the level of the coarctation, Reifenstein and associates (1947) classified the narrowing as moderate when the luminal diameter was 5 mm. or more, and as extreme when the lumen measured 5 mm. or less. Judging from the 104 cases reviewed by these authors and from the 200 reviewed by Abbott (1928), in about one-fourth of the cases the lumen is narrowed moderately, in about one-half the cases it is narrowed extremely and in about one-fourth there seems to be no lumen In the specimens which are removed as part of the operation for coarctation the lumen is rarely more than 2 mm. in diameter Though at times it has been claimed that the lumen is nonexistent, microscopic examination nearly always reveals persistence of a lumen, however tiny

A fallacy frequently encountered in descriptions of the narrowed portion of the aorta is that the aorta has the appearance as though a ligature had been placed around it This fallacy started many years ago. The student of coarctation of the aorta will be interested to read the communication of Craigie, published in 1841,* of coarctation of the aorta in a girl aged seven years and a review of the nine cases of this condition which had been reported up to that time

According to Craigie, Graham reported the second case of coarctation of the aorta, the first having been published by Paris in 1791. Graham described the narrowing of the aorta as having the appearance exactly as though a ligature had been tied tightly around the aorta This seems to be the initial expression of the fallacy. In the ninth case which Craigie reviewed, that of

* The paper of Craigie is recommended for reading since in the review of the first 10 reported cases of coarctation are contained descriptions of many of the features of coarctation of the aorta, including material on the collateral circulation, the occurrence of bicuspid aortic valve, and the ...

Nixon, the patient was a young physician, aged 27 years. The coarctation was described as follows: At the ductus arteriosus the aorta exhibited *a constriction similar to that which would occur if a sharp body had been pressed upon its upper surface until it had diminished the caliber of the lumen* by one-half. Though the narrowing in Nixon's case seems to have been of lesser degree than usual, the description of the aorta is more in keeping with the usual appearance than is the description of Graham.

The importance of the correct description of the gross appearance of the aorta is emphasized because the gross appearance is readily correlated with the microscopic features of coarctation of the aorta.*

Microscopically the basis for the aortic narrowing is a peculiar deformity of the aortic media (Edwards *et al*, 1948*a*) In sections through the zone of coarctation, the media of the cephalic, ventral and dorsal portions of the aortic wall shows a characteristic thickening which projects into the lumen, making it narrow and eccentric In longitudinal sections the localized thickening of the media appears as a curtain (Figures V-77*b* and V-78*a* and V-78*b*) The medial thickening described is seen in cases of coarctation at all ages including the period of infancy (Figure V-78*b*).

When specimens from adolescents and adults are examined there is often an additional change at the zone of aortic narrowing. This takes the form of intimal thickening. The intimal change is particularly prominent over the curtain of thickened media. In longitudinal sections it



Figure V-78 *a* Photomicrograph of the aorta at the level of coarctation Section prepared like specimen illustrated in Figure V-77*b* The proximal portion is to the left, the distal to the right The ligamentum arteriosum inserts into the inferior wall of the aorta proximal to the coarctation The superior wall of the aorta shows characteristic infolding of the media, producing a narrow lumen Overlying the medial curtain is a triangular mass of connective tissue representing secondary intimal thickening Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 4½. (From Edwards *et al*, 1948a)

b Photomicrograph of a longitudinal section through the isthmus of the aorta in the region of the ductus arteriosus, from a male infant that died at the age of 36 days Beyond the isthmus and opposite the entrance of the ductus arteriosus the aorta shows a characteristic curtain-like deformity of the media causing narrowing of the aortic lumen Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 6.

frequently has a triangular shape, its base being attached to the thickened media, its apex directed toward the opposite wall (Figure V-78*a*). It is avascular and is composed largely of collagen laid down in concentric layers. Varying amounts of elastic tissue are present, particularly concentrated in the deeper portions of the tissue. Occasional smooth muscle cells are present as well. Since the intimal thickening at the zone of luminal narrowing is not seen to any extent, if at all, in infancy (Figure V-78*b*), it is interpreted as developing during the life of the patient with

* An opportunity for the microscopic study of an adequate number of aortas with coarctation has been afforded to my associates at the Mayo Clinic and me by the availability of the segments of the aorta removed during operation for this condition by Dr O. T. Clagett. Mrs Karna C. Hood has been particularly helpful in this study by making reconstructions of serial sections prepared by Mrs. Mary Dresbach Noser

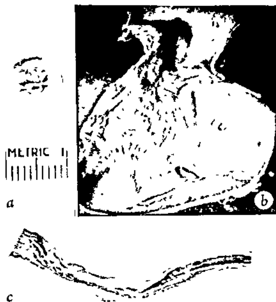


Figure V-79 *a* The distal end of a segment of aorta removed surgically by Dr O T Clagett because of coarctation The lumen is toward the inferior wall and the intima protrudes nipple-like into the lumen of the distal aorta From a female patient 19 years old

b The aorta showing coarctation Immediately inferior to the coarctation there is a jet lesion characterized by a corrugated intimal surface See *c* for photomicrograph

c Photomicrograph of section through the jet lesion shown in *b* The media is interrupted beneath the irregular intima Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 4 From a man 29 years of age

coarctation Moreover, its laminated structure and the presence of most of the elastic tissue in its deeper portions support the concept that localized intimal thickening is developed progressively The cause for its development is probably trauma by eddies of blood at the point of aortic narrowing

Probably as a result of the constant force applied by the blood in the aorta proximal to the coarctation, the intimal tissue protrudes like a nipple into the aortic lumen distal to the coarctation (Figure V-79*a*). This feature is comparable to the protrusion of the pulmonary end of a patent ductus into the lumen of the left pulmonary artery (Figure V-71*d*) The nipple-like protrusion of the margins of the opening in the diaphragm is one of the characteristics which makes it simple for one to distinguish the proximal from the distal end of a segment of aorta with coarctation.

In the light of the histologic features of aortic coarctation, it is interesting to discuss the composition of the diaphragmatic membrane that exists at the site of coarctation, as seen in adolescents and adults. It is composed basically of the localized medial thickening, superimposed on which is the new intimal tissue It is to be emphasized that while the intimal thickening may decrease the diameter of the aortic lumen to some degree, the basic alteration creating obstruction must be charged to the localized deformity of the media.

There has been considerable speculation concerning the structural nature and the *cause of coarctation* of the aorta. Concerning the cause, one of the hypotheses frequently mentioned, even in the very recent literature, is the so-called skodaic hypothesis. The concept was evidently first expressed by Craigie It assumes that the coarctation is caused by an overgrowth into the aorta of the tissue which closes the ductus arteriosus Even without observations on the structural nature of the coarctation there are sufficient objections to the skodaic hypothesis to make it untenable. For example, it does not explain those cases of coarctation in which the aortic stricture lies some distance from the ligamentum arteriosum, nor does it explain the rare cases in which there are two sites of coarctation (Benkwitz and Hunter, 1937). Moreover, coarctation exists at times in the presence of a patent ductus arteriosus. Were the skodaic hypothesis correct, one would expect to find cases of coarctation of the left pulmonary artery as a result of overgrowth of ductal tissue on the pulmonary side. The author is not aware that such a malformation has ever been observed.

Pezzi and Agostoni (1928), on the basis of histologic studies, claimed that smooth muscle which causes the obliteration of the ductus arteriosus invades the wall of the aorta and encircles it. By its proliferation the smooth muscle causes a belt-like constriction of the aorta Bremer (1948), on the basis of studies on pig embryos, expressed the opinion that the so-called adult type of coarctation in human beings was caused by extension of ductal tissue into the aorta. Friedberg (1941) considered coarctation a developmental disturbance of the aorta itself. After studying reconstructions of the aorta and ligamentum arteriosum in coarctation, my associates and I have been unable to satisfy ourselves that in coarctation of the aorta the tissue of the ductus arteriosus has a more intimate or otherwise different relationship to the aorta than in normal (control) conditions. Though, for the time being at least, I have to reject the skodaic hypothesis as to the basis for coarctation of the aorta, I cannot offer an explanation for its cause Since coarctation of the aorta is observed at birth, the condition is to be considered a congenital malformation developing during intra-uterine life

The entire aorta proximal to the coarctation is of normal caliber or, more often, dilated. The wall is thick. Usually the medial elements are normal histologically Harrison (1939) found mucoid medial cysts in the arch of his patient, a 27-year-old man who died of cardiac failure

Distal to the coarctation the aortic wall is thin but the medial elements seem normal on microscopic examination While the descending thoracic aorta is often of normal caliber, the abdominal aorta characteristically is narrow. Beyond the origin of the renal arteries the diameter of the aorta is frequently hardly more than 1 cm. In the thoracic portion are seen wide ostia of the intercostal arteries. This change is particularly noticeable in the case of the upper five to seven pairs of aortic intercostal arteries.

That part of the aorta which lies distal to the coarctation may show a localized lesion characterized by a corrugated patch which rises above the intimal surface (Figure V-79*b*) Microscopically, such a lesion consists of localized fibrous intimal thickening, beneath which there may be distortion of medial architecture (Figure V-79*c*). The lesion appears to result from trauma by a jet of blood striking the wall after passing through the zone of aortic narrowing. As previously mentioned, because of this interpretation of the pathogenesis (Edwards *et al.*, 1948a), this intimal lesion has been called a "jet lesion."

The jet lesion is of significance for several reasons. In the first place, it may lie within that part of the aorta which is anastomosed during the operation for the relief of coarctation. The avascular fibrous intima, if incorporated in the suture line, might act as a foreign body and prevent adequate healing of the surgical anastomosis. In the second place, since there may be loss of elastic tissue in the media beneath the jet lesion it could be conjectured that a saccular aneurysm might develop in this zone. It is conceivable that the jet lesion may also serve as the focus for the origin of a dissecting aneurysm below the level of the coarctation, a complication occasionally observed. It may also represent the point of origin of bacterial aortitis which characteristically starts just beyond the level of the coarctation.

The peculiar association of congenitally *bicuspid aortic valve* with coarctation is unexplained. In the review of Abbott (1928) on the so-called adult type of aortic coarctation, bicuspid aortic valve was reported as occurring in 23 5 per cent of the cases.

In 1937 Benkwitz and Hunter reported that bicuspid aortic valve occurred in 25.3 per cent of the 75 cases of aortic coarcta-

tion that had been reported since Abbott's review. In the interval between the appearance of the paper of Benkwitz and Hunter and that of Lewis in 1945, bicuspid aortic valves were encountered in 37.5 per cent of the cases reported. The communication of Reifenstein, Levine and Gross published in 1947 stated that bicuspid aortic valve occurred in 42.7 per cent of the 104 cases of the so-called adult type of aortic coarctation reported since the time of Abbott's review. Probably one may attribute the apparently increasing incidence of bicuspid aortic valves in cases of coarctation to the emphasis placed on the possible occurrence of this additional malformation by Abbott in 1928 and by others later. One may predict that the reported incidence of bicuspid valves in coarctation will rise in years to come as a result of greater awareness among pathologists of the likelihood of their occurrence.

The *heart* is often enlarged in coarctation of the aorta. In those cases with a closed ductus arteriosus, the hypertrophy is either predominantly or exclusively of the left ventricle. This is explained in part by the occurrence of systolic and diastolic hypertension in the aorta proximal to the coarctation. One other cause of left ventricular hypertrophy is aortic valvular insufficiency in the presence of a bicuspid aortic valve (Figure V-80).

Campbell and Suzman (1947) reported that among 15 clinical cases of aortic coarctation aortic diastolic murmurs were heard in six instances. In one of these cases the murmur was thought to be caused by rheumatic endocarditis; in the other five cases it was thought to be related to the coarctation. Christensen and Hines (1948) reported that 20 per cent of 96 clinical cases with aortic coarctation had diastolic cardiac murmurs usually situated over the base of the heart. They indicated that while such a murmur can be caused by an incompetent bicuspid aortic valve, other conditions such as an associated patent ductus arteriosus, ventricular septal defect and bacterial or rheumatic endocarditis may also give rise to this abnormal physical sign.

Collateral Circulation. The clinical diagnosis of coarctation of the aorta depends in a great measure on demonstrating evidence of the collateral circulation which exists in this condition. For this reason it is pertinent to discuss this feature in coarctation of the aorta in some detail.

According to Craigie, Paris in 1791 and Graham in 1814 reported on the extensive collaterals in this condition. The report of Meckel (1827) is often quoted as an early account on this subject and the diagram in his report has been reproduced by several authors. That this is an important contribution is readily conceded. It should be pointed out, however, that the artist's portrayal that the dilated intercostal arteries caused erosions of the superior aspects of the ribs is probably inaccurate. White (1885) gave an accurate account of the collateral circulation. In the century that followed these works, more data on the collateral circulation were added and these were reviewed in the studies of King (1926), Blackford (1928), and Abbott



Figure V-80. Bicuspid aortic valve. From a man aged 28 years with coarctation of the aorta. Underlying the aortic valve the ventricular face of the anterior mitral leaflet shows a patch of endocardial thickening probably resulting from aortic regurgitation. (From Edwards *et al.* 1948c.)

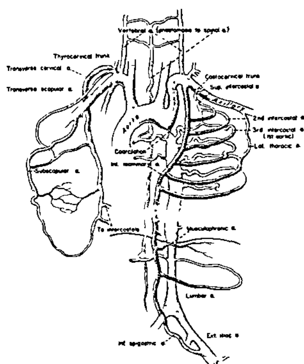


Figure V-81 The collateral circulation in coarctation of the aorta (From Edwards *et al*, 1948b.)

(1928) Important additional contributions have been made by others since the time of these reviews

Rosler (1928) and Railsback and Dock (1929) reported that the defects of the ribs caused by the enlarged intercostal arteries could be demonstrated roentgenographically and that these changes could be used in establishing the clinical diagnosis of coarctation. Substantial evidence concerning the anatomy of the collateral arterial system was supplied by Love and Holms (1939) and Bramwell and Jones (1941).

Using the facts supplied by published accounts and those gained by our own experience, my associates and I (1948*b*) prepared a diagram (Figure V-81) of the collateral circulation in the usual type of coarctation of the aorta in which the ductus arteriosus is closed.

In Figure V-81 the details shown on the left side of the body (the right side of the figure) include the arteries that are essentially part of the thoracic cage, as well as the circulation to the left side of the abdominal wall and to the left lower extremity, while the details on the right side represent the vessels concerned with the circulation of the scapula and adjacent tissues. The details for the left side are applicable to the right as well, and *vice versa* The diagram shows that in the type of aortic coarctation represented, the subclavian arteries, through the communications of their branches, play the paramount role in carrying blood from the part of the aorta above the coarctation to the part below. The common carotid arteries are of minor importance in the collateral circulation in coarctation of the aorta, except in cases with unusual forms of coarctation. The subclavian arteries may be greatly dilated, at times to aneurysmal proportions. Evidence of a pulsating and dilated left subclavian artery may be obtained on roentgenoscopy or by the use of roentgenokymograms (Gladnikoff, 1946, Stauffer and Rigler, 1950) This evidence of coarctation is particularly useful for the roentgen diagnosis of this condition when notching of the ribs is not demonstrable.

The intercostal arteries, with the exception of the first two pairs, are most important anastomotic bridges. This is particularly true of the fourth through the seventh pairs of arteries (Lewis, 1933). These arteries act as bridges through their communication with the aorta below the level of the coarctation on the one hand, and with the internal mammary, musculophrenic, superior epigastric, anterior spinal and lateral thoracic arteries and the descending branch of the transverse cervical artery on the other. In this way the intercostal arteries carry blood which is ultimately derived from the aorta above the level of the coarctation to that portion of the aorta which lies below the coarctation. It is undoubtedly true that the vessels about the scapula, which communicate directly or indirectly with the intercostal

arteries, contribute materially to the function of the collateral system portrayed. Bramwell and Jones indicated that these communications by far overshadow those of the intercostal arteries with the internal mammary artery and its terminal branches. The illustrations from the case they presented support this view. Railsback and Dock, on the other hand, while cognizant of the communications of the intercostal arteries with the arteries of the scapula, stated that in their case the anterior communications of the intercostal arteries with the internal mammary arteries seemed to represent the important avenues of collateral circulation. The internal mammary arteries are consistently dilated and tortuous.

Pulsation of the dilated arteries related to the scapula is a frequent and a clinically valuable diagnostic sign (Walshe, 1873, Blackford, Campbell and Suzman, and others). In an analysis of the clinical features in 96 cases of aortic coarctation, Christensen and Hines noted that evidence of a collateral supply had been sought in 74 patients In 61 of these (82 4 per cent) there was evidence of a collateral circulation on physical examination This was most frequently observed over the scapular and interscapular regions and less frequently in the supraclavicular regions In these regions the collaterals may be felt to pulsate and in some cases murmurs may be heard over the arteries

The intercostal arteries, by virtue of their function, become greatly dilated and tortuous Dorsally in particular, the tortuosity produces pressure atrophy of the adjacent ribs. At times this atrophy takes the form of mere enlargement of the costal grooves of the ribs (Wolke, 1937) (Figure V-82*a*) At other times, at the points of greatest tortuosity there is gross focal erosion of the substance of the rib (Figure V-82*b* and V-82*c*) When this erosion occurs, it represents an important diagnostic



Figure V-82 *a* A rib removed during operation for coarctation, showing irregularity of the contour and enlargement of the subcostal groove From a woman aged 19 years whose aorta is illustrated in Figure V-79*a*

b Posterior portion of a rib in a man, aged 19 years, with coarctation of the aorta The intercostal artery is tortuous (See *c*)

c. The intercostal artery illustrated in *b* has been removed, showing that at the points of tortuosity of the artery, the rib is notched The notches occur in the inferior aspect of the main body of the rib and in the adjacent portion forming the subcostal groove The inferior margin of the rib is not notched (Figures V-82 *b* and *c* from Edwards *et al*, 1948b)

roentgenologic feature in coarctation of the aorta since the notches are readily recognized in roentgenograms of the thorax. It is of interest that although it is commonly stated that the lower margin of the rib is notched in coarctation, this is usually not the case. On the contrary, the notching occurs on the inferior and ventral aspect of the main body of the rib, at the point at which it joins that part of the rib which forms the wall of the costal groove. This pathologic feature was illustrated by Ernstene and Robins (1931). Since the inferior portion of the rib which forms the posterior wall of the costal groove is thin in comparison to the superior portion of the rib, it may be sufficiently penetrated



Figure V-83 Roentgenogram of the thorax in a patient with coarctation of the aorta The white arrows point to the inferior margins of the ribs The black arrows point to the notching in the main body of the ribs (From Pugh, 1948)

by roentgen rays as to become invisible in the roentgenogram Under such conditions, the notching appears to involve the inferior margin of the rib. This picture, however, is an illusion produced by roentgen-ray penetration of the inferior portion of the rib

Crafoord and associates (1947) and Pugh (1948) have pointed out that when roentgenograms of the thorax in patients with coarctation of the aorta are examined carefully, one frequently can demonstrate a portion of the rib inferior to that which is notched, these roentgenographic changes corresponding to changes that are present anatomically (Figure V-83).

Pugh has observed that about one-fourth of patients with coarctation of the aorta do not have roentgenologically demonstrable notching of the ribs. The process of erosion of the ribs must be a progressive one, since the patient without notching is usually a child. In some instances, however, notching is demonstrable in children and in some instances in adults, notching may not be evident In 1939 Brown stated that six years was the youngest age at which notching had been recorded, and Blumenthal and Davis (1941) stated that it had been observed in children as young as five years. Neuhauser (1946) observed this finding in an infant 19 months of age and in a child eight years old.

The reason that the first two intercostal arteries do not play a large role in the collateral system is that they usually do not communicate with the aorta dorsally, as the other intercostal arteries do. Dorsally, the first two intercostal arteries communicate with the superior intercostal artery, which in turn is in communication, either directly or through the costocervical trunk,

with the subclavian artery of the same side. The superior intercostal artery may, however, serve a bridging function by its anastomosis with the third intercostal artery, at a point ventral to the site at which the latter vessel arises from the aorta as the first aortic intercostal artery.

The communication of the two terminal branches of the internal mammary, the musculophrenic and the superior epigastric arteries with the lower intercostal arteries, which occurs ventrally, has already been mentioned. A prominent and additional communication of the superior epigastric artery is that with the cephalic portion of the inferior epigastric artery. Through this channel a substantial amount of blood may be carried from the subclavian artery, proximally, to the external iliac and femoral arteries, distally As judged from the width of this channel and from the narrow state of the lower abdominal aorta, a considerable amount of blood carried to the legs probably avoids the lower aorta entirely. That the amount carried by this channel is great is further supported by the fact that in coarctation of the aorta, in spite of characteristic absence of pulses in the abdominal aorta and in the iliac and femoral arteries, the volume of blood flow to the legs is within normal limits (Wakim *et al.*, 1948).

The position and the communications of the anterior spinal artery are represented in Figure V-81 This artery may serve as a collateral channel in coarctation of the aorta since it lies along the entire length of the spinal cord and so forms a continuous channel past the level of the aortic narrowing By receiving communications from the vertebral arteries in the cervical region, it receives blood derived from the subclavian arteries, which ultimately comes from the aorta proximal to the level of stenosis. Furthermore, by its communications with the intercostal and lumbar arteries in the thoracic and lumbar regions, respectively, the anterior spinal artery may carry blood flowing into it from the vertebral arteries proximally toward the aorta distally.

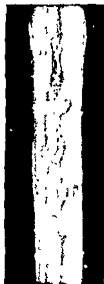


Figure V-84 Lower cervical and upper thoracic portion of the spinal cord of a man aged 19 years with coarctation of the aorta One of the ribs of this patient is illustrated in Figures V-82*b* and *c*. The anterior spinal artery is dilated and tortuous

The role of the anterior spinal artery as a collateral channel has received relatively little attention in the past, although in our experience (Edwards *et al*, 1948*b*) it is often dilated and tortuous in cases of aortic coarctation, particularly in the cervical and thoracic regions (Figure V-84) Evidently, symptoms resulting from the dilated state of the anterior spinal artery are not common.

One exception is the case of Haberer (1903) which is quoted by Herxheimer (1910) and by Abbott. This case is quoted as one of transverse myelitis resulting from compression of the spinal cord by the dilated spinal artery. Review of the

original report of Haberer, however, shows that although the anterior spinal artery was dilated, the paralysis of the lower extremities of the patient, a woman aged 47 years, appeared suddenly and that the necropsy revealed thrombosis of the anterior spinal artery as well as compression of the spinal cord in the upper thoracic region Though Haberer claimed that the myelomalacia was due to compression, the sudden onset of symptoms and the thrombus in the artery suggest that arterial occlusion had a greater influence in causing changes in the spinal cord than did the dilatation. Haberer mentioned a case of Brasch in which slowly developing paralysis resulted from compression of the spinal cord by a dilated and tortuous anterior spinal artery

It is appropriate to judge that the collateral circulation characteristic of aortic coarctation begins during intra-uterine life. n the usual type of aortic coarctation the arctation lies distal to the aortic ostium the ductus arteriosus, whether patent or closed. In the fetus this anatomic arrangement would be incompatible with life unless the coarctation were by-passed by collateral channels. The fact that the fetus may reach full maturity with coarctation lying distal to the aortic mouth of the ductus seems sufficient evidence to support the opinion that a collateral circulation is set up during the fetal life in those cases wherein coarctation lies distal to the ductus. In cases in which the coarctation lies proximal to the ductus a collateral circulation may not develop during fetal life, and in fact intra-uterine life may progress without hindrance in the absence of collaterals. More discussion of these matters will be found in those sections dealing with Coarctation in Association with Patent Ductus Arteriosus.

Functional Disturbances. Brown and associates (1948), who made functional studies on 25 patients with coarc[illegible]on of the aorta, defined the functional characteristics of coarctation of the aorta as follows: (1) The systolic and diastolic pressures in the upper extremities are elevated; (2) the systolic pressure of the lower extremities is normal or reduced, but the diastolic pressure is, as a rule, elevated; (3) the ratios of femoral to radial systolic pressure and of femoral to radial pulse pressure are below the range of similar ratios in normal persons; (4) there is a delay in the onset of a femoral pulse wave as compared with the time of onset of the radial pulse wave, and (5) the period between the onset and the peak of the femoral pulse is usually longer than that observed in normal persons. Stewart and associates (1944) and Bing and associates (1948) discussed the hypotheses as to the basis for hypertension in cases of coarctation of the aorta. One theory holds that the hypertension is caused by the obstruction due to the lesion in the aorta and by the relatively narrow state of the collateral bed. Another cause given is that there is a generalized increase in peripheral resistance, possibly resulting from pressor substances eliminated by the kidneys inadequately supplied with blood. As yet, there is conflicting opinion as to the basis for hypertension. It might be that several causes operate together rather than only one.

Complications. Although coarctation of the aorta may occasionally allow a patient to achieve a full span of life, it often causes death prematurely. Before complications develop, the patient frequently has no disability and may partake in arduous labor. Newman (1948) reported on 23 patients who had served in the British military forces. Baber and Daley (1947) reviewed 43 reported instances of pregnancy in coarctation and stated that as a rule cardiac compensation was maintained.

Of 104 fatal cases of the so-called adult type of coarctation, in which the ratio of

males to females was 5:1, Reifenstein and associates found that 61 per cent of the patients died either before or during the fortieth year of life. The average age at death was 35 years. Three-quarters of the patients died as a result of the malformation, the remaining one-quarter from unrelated causes. The four common fatal complications are: left ventricular failure, bacterial endocarditis or aortitis, dissecting aneurysm of the aorta and rupture of an aneurysm of the circle of Willis. Left ventricular failure results either entirely or in part from the existing hypertension. Insufficiency of the bicuspid aortic valve may contribute to left ventricular failure. In Reifenstein's series 18 per cent of the patients died of *congestive cardiac failure*, the average age at death in this group being 39.3 years.

Bacterial endocarditis usually develops upon a bicuspid aortic valve as in the cases of Kellogg and Biskind (1934), Wechsler and Gustafson (1937), and Hallock and Hebbel (1939) (Figure V-85*a*). Bacterial endocarditis accounts for death in about one-fifth of the cases of aortic coarctation (Abbott, 1928, Blackford, 1928, Reifenstein *et al.*, 1947). Other foci of intravascular infection occur but are less common. Reifenstein, Levine and Gross reported that among 104 cases, two showed bacterial aortitis involving the ascending aorta and four other cases showed similar lesions just distal to the coarctation.

Bauer and Iverson (1945) reported on two cases without bacterial endocarditis but with *bacterial aortitis* and *mycotic aneurysm* originating just beyond the coarctation. In one case the aortic aneurysm ruptured. In the other case there were multiple secondary mycotic aneurysms of abdominal arteries. One of these, which involved the superior mesenteric artery, ruptured. Bauer and Iverson stated that there were in the literature 10 other cases of primary bacterial aortitis complicating coarctation. The ages of the patients varied from six to 38 years, the oldest patient being that of Koletsky (1942).

In other patients an aortic mycotic aneurysm, either proximal or distal to the





Figure V-85. *a* Bacterial endocarditis complicating a bicuspid aortic valve in a man aged 25 years with coarctation of the aorta. *b* The left ventricle and aorta of a woman aged 34 years with aortic coarctation. Beyond the origin of the dilated left subclavian artery the aortic lumen narrows sharply and characteristically. In the ascending aorta, above a bicuspid aortic valve, there is a rent characteristic of dissecting aneurysm. Rupture of the aorta into the pericardial sac caused death. (The case is that of Dr. Timothy Leary of Boston. Illustration reproduced with his permission.)

coarctation, may be secondary to a complicating bacterial endocarditis.

Rupture of the aorta other than that resulting from localized bacterial infections is also a common cause of death. The most frequent lesion in this group is *dissecting aneurysm* originating in the ascending aorta (Figure V-85*b*). It causes death in about 17 per cent of cases of coarctation. In a smaller group a fatal aortic dissecting aneurysm originates distal to the coarctation

Examples of cases of aortic coarctation complicated by dissecting aneurysms include those of Binder (1919), Boyd and Werblow (1937), Regester and Innes (1938), Black (1942), and Lewis (1945) Usually a dissection starting in the ascending aorta or arch terminates at the level of the coarctation and rupture occurs into the pericardial sac The case of Boyd and Werblow was unusual in that the dissection, starting in the ascending portion of the aorta, extended to involve the iliac arteries.

Rupture of the aorta distal to the coarctation may result from a mycotic aneurysm, from a bland *saccular aneurysm* or from a dissecting aneurysm originating distal to the coarctation Mycotic aneurysms of the distal portion of the aorta may occur as a complication of bacterial endocarditis or may result from primary bacterial aortitis. It is to be emphasized that, in the absence of infection, rupture of the aorta distal to the coarctation is rare. Moragues and associates (1942) stated that up to the time of their communication only five cases of rupture of the aorta distal to coarctation had been reported. In their case, in which the patient was a boy aged 11 years, there was a saccular aneurysm just beyond the coarctation. This had ruptured into the esophagus. In Hecker's patient (1939), a man aged 62 years, there was a dissecting aneurysm of the descending aorta. The patient of Zaslow and Krasnoff (1943), a man aged 25 years, had a fusiform aneurysm of the descending aorta which ruptured into the left pleural cavity. These authors suggested that eddy currents in the blood just distal to the coarctation may have caused gradual weakening of the aorta with formation of aneurysm. This opinion, probably correct, was expressed despite the occurrence of the mucinous cysts in the media of the aorta. Blickman (1949) expressed the opinion that localized formation of bland aneurysm beyond the coarctation is the result of primary deficiency in the structure of the aorta rather than of localized trauma as postulated by my associates and me (Edwards *et al*, 1948a) Clark and Koenig (1947) reported on the roentgenologic and pathologic features of an unruptured bland saccular aneurysm of the descending aorta in a woman 25 years old

Alexander and Byron (1944) excised an aneurysm of the descending aorta in a 19-year-old youth with coarctation of the aorta Shumacker (1948) reported an excision, in a boy aged 8½ years, of a similar aneurysm below the coarctation and performance of an end-to-end suture of the aorta At the Mayo Clinic, Dr. O. T. Clagett performed similar procedures in a 24-year-old woman. The aneurysm (Figure V-86*a*), though continuous with the aorta, seemed to arise from an intercostal artery rather than from the aorta proper. Halonen and Aho (1949) described two cases of aortic coarctation complicated by saccular aneurysm just beyond the constriction. One occurred in a woman aged 39 years, the other in a man aged 20 years; in the latter case, the aneurysm ruptured.

Abbott observed that *neurologic lesions* were present in 25 of the 200 cases which she reviewed. In 20 of these there was an intracranial hemorrhage. This usually results from *rupture of an aneurysm of the circle of Willis* (Figure V-86*b*). In five of



Figure V-86 *a* Photomicrograph of a specimen of aorta removed surgically for coarctation by Dr O T Clagett The aorta has been oriented and sectioned like the aortas in Figures V-77*b* and V-78 The proximal portion of the aorta lies to the left The aortic end of the ligamentum arteriosum blends with the lower surface of the aorta Immediately distal to the ligamentum the superior wall of the aorta shows the characteristic medial deformity causing coarctation An aneurysm involving the descending aorta and the mouth of an intercostal artery is present Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 4.

b. The circle of Willis in a man aged 28 years with coarctation of the aorta Two aneurysms, neither of which has ruptured, are present The aortic valve of this patient is illustrated in Figure V-60 (From Edwards *et al*, 1948a)

Abbott's cases other types of neurologic lesions were observed. These included cerebral emboli and rare involvement of the spinal cord, as in the case of Haberer, to which reference has been made in the discussion on the collateral circulation In 104 cases reviewed by Reifenstein and associates 13 patients had intracranial lesions In nine instances the brain was examined and a ruptured aneurysm of the circle of Willis was found in five instances. Examples are the cases of Davies and Fisher (1943) and of Wright (1949) In two patients there was subarachnoid hemorrhage but an aneurysm was not found. One patient had lesions caused by cerebral atherosclerosis, and in one patient embolism to the brain complicated an aneurysm of the aorta. This compilation of cerebral complications of coarctation does not include those cases in which bacterial endocarditis was present.

In the case of Clark and Firminger (1949), in which the patient was a man aged 31 years, complete heart block and Adams-Stokes syndrome were associated with calcific stenosis of a bicuspid aortic valve Reifenstein and associates reported that among 93 cases of coarctation of the aorta in which the pathologic descriptions were adequate, *calcification of bicuspid aortic valves* was present in 11 instances. Moore and Dimond (1946) described a case in which the Wolff-Parkinson-White syndrome was observed in a boy aged 15 years with coarctation The association was considered coincidental

The effect of surgical therapy of coarctation of the aorta on the incidence and occurrence of *complications* is as yet unknown. On the basis of certain features of coarctation some predictions can, however, be made. The elimination of hypertension will undoubtedly lessen the tendency to cardiac failure It is to be emphasized, however, that in those patients with pronounced cardiac hypertrophy, significant reduction in the size of the heart will

probably not follow surgical treatment. In these persons, as in all who have cardiac hypertrophy for any reason, cardiac failure may be encountered.

The incidence of dissecting aneurysm of of the aorta will, in all probability, fall considerably as essentially normal blood pressure levels are attained.

In view of the high incidence of bicuspid aortic valve in patients with coarctation of the aorta, bacterial endocarditis will probably continue to be a complication of significant incidence It is conceivable that some reduction in the incidence of bacterial endocarditis will result among patients who achieve normal blood pressure levels, but it is anticipated that even they will not be immune from this complication.

With attainment of blood pressure readings within the normal range, the incidence of ruptured intracranial aneurysms will, in all probability, fall. Nevertheless, in some patients surgically cured of the coarctation, subarachnoid hemorrhage may at some future date result from rupture of an aneurysm that already existed at the time of the operation.

Coarctation in Unusual Locations. Stenosis of a Subclavian Artery. Clinical recognition of an unusual location of coarctation of the aorta or of the association of stenosis of one of the subclavian arteries usually depends upon demonstration of significant differences in the blood pressures of the two arms (Weber and Knop; 1929; East, 1932; King, 1937, Bagley and Holoubek, 1940; Schwartz and Greene, 1942; Burchell *et al.*, 1950).

The collateral channels are larger on the side with the elevated brachial blood pressure than on the opposite side, particularly as indicated by notching of the ribs (Love and Holms, 1939) though, as Burchell and associates and others have noted, notching may at times not be apparent on either side.

In reviewing the blood pressure readings in 170 cases of coarctation, King observed that in nine patients the left brachial systolic blood pressure was normal while the right was elevated. In four of these, however, the left brachial diastolic pressure was elevated. King added a tenth clinical case. The most common atypical form is exemplified by cases of Parker and Dry (1938), Bing and associates (1948), and Sanes, Juvelier and Bahn (1950), in which the coarctation was situated between the origins of the left common carotid and left subclavian arteries. This produces low systolic pressure in the left arm and elevated systolic pressure in the right arm. The ribs on the right side may show notching while those on the left do not. A similar clinical picture may be produced by *stenosis of the first part of the left subclavian artery* (Bedford, quoted by Weber and Knop, 1929), or by *hypoplasia of the left subclavian artery* (Woltman and Shelden, 1927), in either case the narrowing of the aorta being in the vicinity of the ligamentum arteriosum.

In those cases with low systolic blood pressure in the right arm as contrasted to that in the left, the malformations may take one of two forms. In each the coarctation lies in the usual location, in the vicinity of the ligamentum arteriosum In one form, as reported by Love and Holms (1939), there is stenosis of the orifice of the right subclavian artery as it arises from the innominate artery. In the second form the right subclavian artery arises independently from the aorta below the level of the coarctation. Examples of the latter type are those of Fawcett, Case 12, (1905) and of Stephens (quoted by Gross, 1950). Grishman and associates (1944) described the roentgenographic features in cases of aortic coarctation with absence of the left radial pulse.

Rarely, instances of narrowing of the abdominal aorta are reported as examples

of coarctation of the aorta in unusual locations (Kondo *et al.*, 1950). Whether such cases should be classified as coarctation will depend upon histologic demonstration of the same type of medial malformation as occurs in the classic forms of coarctation of the aorta.

Coarctation of Aorta with Patent Ductus Arteriosus

In approximately 10 per cent of cases coarctation of the aorta is associated with patent ductus arteriosus. The functional disturbances in these cases depend primarily on two factors, at times interrelated, as follows: (1) the location of the coarctation with respect to the aortic mouth of the ductus, and (2) the presence or absence of collaterals.

Coarctation Distal to the Aortic Mouth of Patent Ductus Arteriosus (Figure V-87*a*, *b* and *c*). Whenever a patient exhibits coarctation of the aorta at a point distal to the aortic mouth of a patent ductus arteriosus, the functional disturbances characteristically are those of the ordinary type of coarctation of the aorta in addition to those of patent ductus arteriosus. A potential difference is that the effects of the patent ductus are accentuated as compared with cases of uncomplicated patent ductus arteriosus. There is also a greater chance of right ventricular strain and hypertrophy (Burchell, 1948). Edwards and associates (1949) reported on the pulmonary vascular changes in two cases in which aortic coarctation lay distal to the aortic mouth of a patent ductus arteriosus. The pulmonary arterioles, and particularly the intrapulmonary arteries, were greatly thickened and exhibited corresponding luminal narrowing. Though medial hypertrophy was an element, intimal fibrous proliferation was the outstanding morphologic change. The changes observed were qualitatively like those seen in an ordinary case of patent ductus arteriosus com-

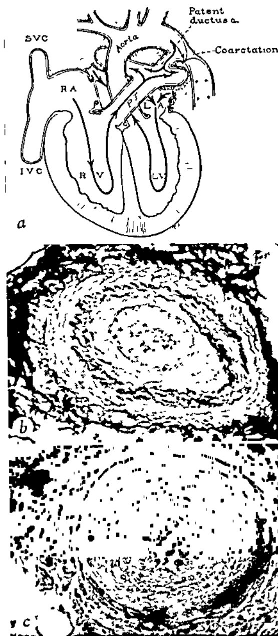


Figure V-87 *a* Coarctation of the aorta distal to the aortic mouth of a patent ductus arteriosus

b An intrapulmonary artery from a girl 15 years old with coarctation of the aorta distal to a patent ductus arteriosus. There are medial hypertrophy and intimal fibrosis causing pronounced luminal narrowing. Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 225

c Intrapulmonary artery from a man 22 years old with coarctation of the aorta distal to a patent ductus arteriosus. There is pronounced cellular proliferation of the elements of the wall, causing corresponding luminal narrowing. Focal hyalinization of the media. Hematoxylin and eosin X 260 (Figures V-87*b* and *c* from Edwards *et al.*, 1949. Reproduced by permission of The C. V. Mosby Company.)

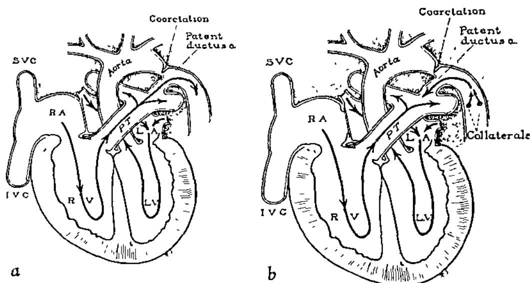


Figure V-88 *a* The circulation in patent ductus arteriosus distal to coarctation of the aorta without collaterals (From Edwards *et al*, 1949 Reproduced by permission of The C V Mosby Company)
b The circulation in patent ductus arteriosus distal to coarctation of the aorta with collaterals (From Taylor *et al*, 1950)

plicated by pulmonary vascular changes, but were more severe and widespread.

In one of the two cases there was pronounced hypertrophy of the right ventricle and during life there had been intermittent cyanosis of the left hand It was interpreted that the occlusive lesions in the pulmonary arteries had caused the resistance to pulmonary blood flow to be greatly elevated In the case cited it appeared that at certain times, at least, the resistance to pulmonary blood flow was greater than the resistance to systemic blood flow. When this happened the right ventricle had evidently assumed the functions of a systemic ventricle and had forced blood from the pulmonary arterial system into the aorta.

Taylor and associates (1950) described the case (Case 1) of a man aged 27 years in whom operation confirmed the clinical impression that coarctation of the aorta lay distal to the aortic mouth of the patent ductus arteriosus. Preoperative studies revealed elevated pulmonary pressures of 61 mm. of mercury systolic and 41 mm. diastolic. The flow through the ductus arteriosus measured 4.8 liters per minute. In this case the flow seemed to be entirely from the aorta to the pulmonary arterial system, since the femoral and radial arterial pressures were significantly higher than the pulmonary pressures, and the systemic arterial blood was 97 per cent saturated with oxygen Six months following ligation of the ductus arteriosus the pulmonary arterial pressures were within limits of normal as follows: systolic, 33 mm. and diastolic, 12 mm. of mercury. In view of the favorable response of the pulmonary arterial pressures it may be assumed that in Taylor's Case 1, pulmonary vascular changes were either minimal in degree or focal in distribution.

Coarctation Proximal to Aortic Mouth of Patent Ductus Arteriosus (Figure V-88*a* and *b*). Coarctation of the aorta proximal to a patent ductus arteriosus is to be distinguished both anatomically and functionally from coarctation of the aorta with patent ductus arteriosus in which the ductus enters proximal to the coarctation. Coarctation of the aorta proximal to a patent ductus arteriosus must *be further subdi-*

vided into those cases with an established collateral system bypassing the coarctation and those cases in which no significant collaterals exist. The latter will be discussed first.

Coarctation of Aorta Proximal to Patent Ductus Arteriosus Without Collaterals (Figure V-88*a*). In the normal fetus the right ventricle supplies the lungs and, through the ductus arteriosus, it supplies the descending aorta as well Probably little blood flows through the isthmus of the aorta, so that the greater part of the blood in the descending-aorta has come to it from the right ventricle In patients in whom coarctation of the aorta develops proximal to a patent ductus arteriosus, fetal life goes on in an essentially normal manner. Ordinarily the stimulus is absent for the development of collaterals, as in those cases in which the coarctation lies distal to the ductus (Evans, 1933)

In the absence of a developed collateral system these patients are subjected to considerable danger after birth, as the ductus arteriosus undergoes normal obliterative processes With closure of the ductus and in the absence of an established collateral system, there probably is deficient flow of blood to the lower part of the body Early death, which is so common in these cases, is probably explained on the basis of such a combination of circumstances. This was probably the basis for death in the patient of Kesson (1948) In a few cases, however, a patent ductus arteriosus is retained and in these the postnatal circulation resembles, in a measure, the fetal circulation. The chief point of resemblance lies in the fact that the right ventricle continues to supply blood simultaneously to the lungs and to the descending aorta

My associates and I (1949) reviewed the morphologic and functional characteristics of coarctation of the aorta associated with patent ductus arteriosus. In the two cases in which the coarctation lay proximal to



Figure V-89 Intrapulmonary arteries in patent ductus arteriosus distal to coarctation of the aorta without collaterals

a. Hypertrophy of muscular arteries of lung From a girl seven years of age Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 55.

b Small muscular artery showing medial hypertrophy From a girl aged seven years Verhoeff's elastic tissue stain, counterstained with van Gieson's connective tissue stain X 435

c. A small muscular pulmonary artery or arteriole showing pronounced cellular thickening of the wall, causing almost complete obliteration of the lumen From a girl 23 months old Hematoxylin and eosin X 460 (Figures V-89*b* and *c* from Edwards *et al*, 1949 Reproduced by permission of The C V Mosby Company)

the patent ductus (one patient was seven years old, the other two years old), there were remarkable changes in the intrapulmonary arteries. These were characterized primarily by medial hypertrophy of the muscular arteries of the lung (Figure V-89*a* and *b*), so that the intrapulmonary arteries resembled systemic arteries. In addition some intimal fibrosis further nar-

rowed the lumen of the arteries (Figure V-89*c*). There was considerable right ventricular hypertrophy. In the seven-year-old patient the ventricular septum was intact The thickness of the two ventricles was equal, a characteristic also seen in the normal fetal heart. Since in this patient the blood pressure in the lower extremities had been of normal systemic character and since the lungs were supplied by the same propelling force as was the lower part of the body, we assumed that pulmonary hypertension had existed. Our interpretation was that the thick muscular arteries of the lungs constituted a carry-over into postnatal life of the same morphologic characteristics as seen in the fetal pulmonary arteries The increased resistance to pulmonary blood flow caused by the pulmonary vascular changes was probably responsible for a balanced distribution of the right ventricular blood to the lungs on one hand and to the lower part of the body on the other.

The interpretations as to the functional disturbances in our cases are supported by observations of Taylor and associates (1950). In the discussion of their communication they described the case of a child aged three years in whom there was evidently a coarctation of the aorta proximal to a patent ductus arteriosus, and associated with this, stenosis of the left subclavian artery. Functional studies revealed pulmonary hypertension and incomplete saturation of blood in the lower extremities. These observations supported the conclusion that the right ventricle was supplying blood both to the lungs and to the lower part of the body. It is pertinent to mention that in this clinical case of Taylor and associates, pulmonary vascular changes such as were observed in the two fatal cases are to be expected.

Swan and associates (1949) described the case of a girl aged 18 years with congenital mitral stenosis and coarctation of the aorta proximal to a patent ductus arteriosus. The intrapulmonary arteries showed structural changes like those which my associates and I described in cases with coarctation proximal to a patent ductus arteriosus.

It is to be recognized that the condition under discussion has functional characteristics similar to those seen in other conditions in which the same ventricular propelling force simultaneously supplies blood both to the lungs and to the systemic circulation and in which there is no pulmonary stenosis. These conditions include the Eisenmenger complex, cor triloculare biatriatum, persistent truncus arteriosus Type I (Collett and Edwards), and tricuspid atresia (Type II*b* (Edwards and Burchell)

Complete interruption of the aortic arch (Sewart, 1948) is a rare condition that developmentally is probably different from coarctation of the aorta with patent ductus arteriosus in which the coarctation lies proximal to the ductus, but functionally the two conditions are identical. This condition is characterized by complete interruption of the continuity of the aorta between the origin of the left subclavian artery and the entrance of the ductus arteriosus The lower part of the body is supplied by the ductus It is possible that the almost universal absence of this condition in adult patients is related to closure of the ductus in the postnatal period, which is followed by death because of inadequate collateral supply between the aortic arch and the descending aorta.

Coarctation of Aorta Proximal to Patent Ductus Arteriosus with Collaterals. In addition to the cases of Taylor and associates mentioned in the paragraphs immediately preceding, these authors reported a third case (Case 2) of coarctation of the aorta in which the coarctation lay proximal to a patent ductus arteriosus (Figure V-88*b*). On cardiac catheterization the catheter

passed from the pulmonary trunk into the descending aorta. Catheterization studies revealed that while there was pulmonary hypertension, the pulmonary blood pressure, though considerably above normal, was lower than the blood pressure in the descending aorta. Oxygenated blood was entering the pulmonary arterial system from the aorta through the patent ductus arteriosus. This direction of flow is obviously different from that in the cases in which the right ventricle supplies both the lungs and the lower part of the body It can be explained only on the basis of collaterals having developed to such a degree as to allow the descending aorta to receive considerable blood from the aorta proximal to the coarctation This in turn is associated with femoral blood pressures of greater magnitude than the pulmonary This phenomenon is associated with the flow of oxygenated blood from the descending aorta into the pulmonary arterial system.

Haxton and Thomson (1948) reported on a girl aged seven years with typical clinical and roentgenographic signs of coarctation of the aorta. The finding of right axis deviation suggested the presence of a patent ductus arteriosus as well. At operation this proved to be the case. The coarctation was found about 1 cm. beyond the origin of the left subclavian artery. The aortic mouth of the patent ductus arteriosus was described as being "near" the coarctation but the accompanying drawing portrays the ductus entering the aorta distal to the coarctation. In many ways, the condition, coarctation of the aorta proximal to patent ductus arteriosus with systemic collaterals, functions like coarctation of the aorta distal to patent ductus arteriosus However, in the latter condition, systemic blood enters the pulmonary system from that part of the aorta proximal to the coarctation and in the former from that part of the aorta distal to the coarctation.

In the third case of Ulrich (1932) the patient was a man 23 years of age. The coarctation was described as being opposite the aortic mouth of a patent ductus. A probe could readily be passed from the ductus into the descending aorta. Systemic collaterals were well developed. It is conceivable that Case 2 of Taylor and associates had similar anatomic features.

VASCULAR RINGS

By common usage the term "vascular rings" refers to those malformations of the aortic arch system which are responsible for interference with the function of the trachea and the esophagus. In this section will be discussed these malformations as well as those that are developmentally related to them Coarctation of the aorta and persistent patent ductus arteriosus have been covered in another section and will not be considered here In most, but not all, of the malformations to be covered the cardiac development is normal and the ductus arteriosus also closes normally Nevertheless, the ductus arteriosus or the ligamentum arteriosum plays an important role in causing the vascular rings. Therefore, there will be much discussion of the position and attachments of the ductus arteriosus Unless specifically stated, use of the term "ductus arteriosus" will imply a normally closing or closed ductus arteriosus.

A variety of anatomic classifications have been offered for the malformations of the aortic arches. One objection to most of these is that they do not include those malformations in which the ductus arteriosus or the ligamentum arteriosum is on the right side. In actual practice

it is difficult to supply a classification which is all-inclusive. Nevertheless, in an earlier publication (Edwards, 1948a), I presented a classification, which despite its shortcomings is workable. In presenting my ideas in support of the classification, I pointed out that for a comprehensive understanding of the malformations of the derivatives of the aortic arch system, it is desirable that the various forms be recognized as bearing some developmental relationship to each other In this way undescribed forms might be considered as hypothetical possibilities and these, if encountered, would be understandable I pointed out that the various malformations could be related to the aortic arch system portrayed in the standard Rathke diagram of the six pairs of aortic arches, that by obliteration or disappearance of certain parts of this system, the various known forms could be derived and certain forms as yet undescribed could be anticipated.

The shortcomings in the use of the Rathke diagram were pointed out These included the fact that important changes in the shape and relations of the arch system occurred between the times portrayed by the diagram and the time of birth. Some of these changes were due either to different rates of growth of the various parts of the system or to adaptation to the shape of other structures developing in the mediastinum One other possible cause of confusion is that in the stages portrayed in the Rathke diagram the subclavian artery lies caudad to the sixth aortic arch which is to form the ductus arteriosus, while by the time of birth the subclavian artery lies in a position cephalad to the ductus arteriosus. It would, therefore, be preferable to use a pattern which had retained those parts of the primitive aortic arch pattern that are necessary for an understanding of the subject and which at the same time had gone through the adjustments of growth and the shift of the subclavian artery to its definitive position, cephalad to the ductus arteriosus. For such a form I proposed using a malformation known as the double aortic arch. Two types of double aortic arches were employed. In one the descending aorta and the ductus arteriosus were each on the left side and in the other the descending aorta and the ductus arteriosus were on the right side. Even this approach has shortcomings, since it does not take into account those rare cases in which the descending aorta and the ductus arteriosus are on contralateral sides of the body. Kirklin and Clagett (1950) essentially extended this classification to overcome these deficiencies. The classification that follows is modified from the one proposed by them.

In it a more primitive and hypothetical form of double aortic arch is used as a basic pattern. From this all the known patterns of the aortic arch system may be derived The proposed basic pattern, illustrated in Figure V-90*a*, is a double aortic arch in which there is both a left and a right ductus arteriosus. In the basic pattern the descending aorta is in a neutral position but in the development of the forms derived from the basic pattern the descending aorta deviates to one side or the other. In addition, by either atresia or disappearance of certain parts of the basic pattern, the various patterns of the aortic arch system may be derived and related to one another With rare exceptions the ductus arteriosus on one side disappears, and the descending aorta deviates to one side. Four basic subgroups thus result. For each there exists a double aortic arch with position of the ductus and the descending aorta peculiar to the particular subgroup. When the descending aorta deviates to the right, it has the following characteristics. The upper portion of the descending aorta lies on the right side of the thorax, to the right of the

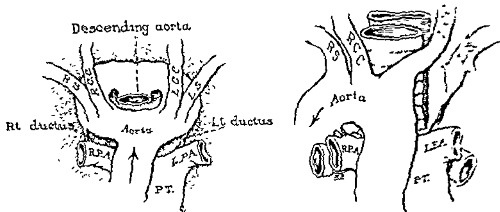


Figure V-90 *a* Double aortic arch and double ductus arteriosus This is a hypothetical form representing the basic pattern from which the various anatomic forms of the aortic arch system may be derived *b* Ghon's case of double ductus arteriosus There is a right aortic arch and right descending aorta, a right ductus which inserts into the right arch, and the left subclavian artery is attached to an obliterated left-sided ductus arteriosus (Modified from illustration of Ghon)

esophagus. In the lower part of the thorax, usually at the level of the body of either the eighth or ninth thoracic vertebra, the aorta crosses to the left behind the esophagus and then emerges from the thorax through the aortic hiatus of the diaphragm.

Classification

- Basic pattern. Double aortic arch and double ductus arteriosus
- *Subgroup A.* Left-sided ductus arteriosus and left-sided descending aorta
- *Subgroup B.* Left-sided ductus arteriosus and right-sided descending aorta
- *Subgroup C.* Right-sided ductus arteriosus and right-sided descending aorta
- *Subgroup D.* Right-sided ductus arteriosus and left-sided descending aorta.

Basic Pattern: Double Aortic Arch and Double Ductus Arteriosus

As far as I am aware, no case of a functioning double aortic arch with bilateral ductus (Figure V-90*a*) has been described, but malformations which are closely ... lated to it are known.

The case of Breschet, which ... produced as Figure 30 in Pou... graph on aortic and arterial ... (1916), showed an obliterated ... each side. The aortic arch ... otherwise normal. The left ... tended from the left pulmonary ... the aortic arch beyond the ... ostium of the left subcl... right ductus extended from ... monary artery to the right ... tery, the latter artery ... the innominate artery ... right side. This malform... the functioning double ... lateral ductus arteriosus ... manner. The right arch ... appeared dorsal to the ... right ductus arteriosus ... aorta deviated to the l...

The case of Ghon (F... there was but one ao... on the right side and ... was likewise on the ... V-90*b*) Three bran... aortic arch. Ventrod... these was as follows:

artery, right common carotid artery and right subclavian artery. An obliterated right-sided ductus arteriosus extended from the right pulmonary artery to the right aortic arch. The left subclavian artery had no connection with the aorta. It was pictured as an artery with a blind proximal end into which a left-sided obliterated ductus arteriosus inserted This case is related to the functioning double aortic arch of the basic pattern as follows: The left aortic arch was lost in two places: ventrally, between the origins of the left common carotid artery and the left subclavian artery, and dorsally, dorsal to the aortic insertion of the left-sided ductus arteriosus. In Ghon's case, in which the left ductus was obliterated, the left subclavian artery could have been supplied by collateral arteries, probably mainly from those originating in the contralateral subclavian artery

Poynter mentioned the cases of Hildebrand and of Holst in which the *left subclavian artery* arose from a *patent ductus arteriosus*. These cases are evidently like that of Ghon, with the exception that in them the ductus remained patent.

On the basis of the very few cases of bilateral ductus arteriosus recorded in the literature, it may be deduced that this type of malformation is indeed rare. Yet it is interesting to note that the case most recently described was reported in 1908. Perhaps in modern days dissections at necropsy are not done with the care that characterized the technics of the older workers.

Subgroup A: Left-sided Ductus Arteriosus and Left-sided Descending Aorta

The vast majority of the patterns of the aortic arch system belong to this subgroup of the basic pattern. They are characterized by a left-sided ductus and left-sided descending aorta. These are related to the

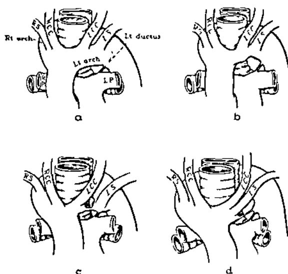


Figure V-91 Vascular rings, subgroup A (Left ductus, left descending aorta) (From Edwards, 1948b Reproduced by permission of the W B Saunders Company)

a Functioning double aortic arch in which the two arches are of about equal size

b Functioning double aortic arch in which the left arch is smaller than the right

c A double aortic arch with atresia of the left arch between the left common carotid and left subclavian arteries (Hypothetical form)

d Double aortic arch with atresia of the left arch between the ductus arteriosus and the origin of the left subclavian artery.

double aortic arch of the basic pattern as follows: The right ductus disappears and the descending aorta deviates to the left. The functioning double aortic arch of subgroup A illustrated in Figure V-91*a* represents a basic pattern from which all members of subgroup A may be derived

1. Functioning Double Aortic Arch (Figures V-91*a* and *b*). The double aortic arch has the following characteristics: The ascending aorta arises normally from the left ventricle and then divides into two arches, a left and a right. The left or so-called anterior arch follows closely the course of the normal aortic arch. It passes in front of the trachea and over the left major bronchus to join the descending aorta which lies on the left side of the body. The right or so-called posterior arch passes over the right major bronchus and then turns rather abruptly to the left dorsal to the esophagus and ventral to the vertebral

column. It joins the left arch either to the left of, or dorsal to, the esophagus at the point at which the latter arch joins the descending aorta The branches of the aortic arches are symmetrically arranged. The right common carotid and the subclavian arteries arise independently, in that order, ventrodorsally from the right aortic arch. Similarly, the left common carotid and subclavian arteries arise from the left arch. The ductus arteriosus is inserted into the left arch between the origin of the left subclavian artery ventrally, and the junction of the left and right arches dorsally. The inferior attachment of the ductus arteriosus is to the left pulmonary artery

It is evident that in the case of functioning double aortic arch the trachea and esophagus are encircled by a vascular ring composed of the bifurcation of the ascending aorta ventrally, the right and the left aortic arches laterally, and either the posterior limb of the right aortic arch alone or the junction of the two arches, dorsally If the vascular ring is sufficiently tight to compress the two tubes which it encircles, the trachea is usually compressed at each side and is thus converted into a triangular-shaped tube at the level of the arches. The esophagus is compressed dorsoventrally The connections of the ductus arteriosus are such as to hold the bifurcation of the pulmonary trunk tightly against the ventral aspect of the trachea, which increases the pressure of vessels against this tube

This appears to be particularly true if the posterior junction of the left and right aortic arches is dorsal to, rather than to the left of, the esophagus. In such instances there is greater tension upon the ductus arteriosus, which in turn, tends to pull the bifurcation of the pulmonary trunk more firmly against the ventral surface of the trachea.

When a functioning double aortic arch exists, the two arches are often of unequal diameter; the right one usually is the wider (Figure V-91*b*) (Curnow, 1875; Blincoe *et al.*, 1936, Wolman, 1939; Herbut, 1943, Case 11; Neuhauser, 1946, Sweet *et al.*, 1947, Case 1; Gordon, 1947, Case 3). Occasionally the two arches may be of approximately equal caliber (Schall and Johnson, 1940, Crystal *et al.*, 1947). I have personally observed an example of this defect. In still other instances, the left arch may be the larger of the two. This was the situation in a case which was reported by Gordon (1947, Case 4)

While double aortic arch may be found in the other subgroups, that of Subgroup A is by far the most common type of double aortic arch, as indicated from the cases reviewed by Griswold and Young (1949).

2. **Focal Atresia of One Aortic Arch.** An accentuation of the inequality of the two aortic arches leads to anomalies in which part of one of the arches is atretic and resembles a fibrous cord. As a rule, the atresia is situated in the left arch but it is a hypothetical possibility that portions of the right arch, instead, may be atretic. In general, three anatomic forms may represent this subgroup, depending upon the site of the atretic segment of the left arch. Hypothetically, the atresia may involve that part of the left aortic arch which lies between the origins of the left common carotid artery and the left subclavian artery (Figure V-91*c*), it usually lies between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus (Figure V-91*d*) (Thomson, quoted by Turner, 1862; Brigham, 1922; Ewald, 1926, Arkin, 1936; Griswold and Young, 1949, Case 1), or it may involve the most distal part of the left arch, between the aortic insertion of the ductus arteriosus and the region of the posterior junction of the left and right aortic arches (Watson, 1877).

3. Right-sided Aortic Arch with Retro-esophageal Segment and Left-sided Descending Aorta. In cases of double aortic arch in which a portion of one arch is atretic but recognizable, it is evident that the atresia occurred rather late during fetal life or after birth. Should the process of obliteration of a portion of a double aortic arch occur relatively early in fetal life, it is possible that the atretic segment would no longer be present as an identifiable structure at the time of birth. The double arch would cease to exist as a continuous structure. Such variants of the double aortic arch are included in the following forms.

a *Right-sided aortic arch with retro-esophageal segment and left-sided descending aorta, left subclavian artery originating from aortic diverticulum* If that segment of the left aortic arch between the origin of the left common carotid artery and the left subclavian artery disappears, the following aortic arch pattern is achieved (Figure V-92*a*). There is but one complete aortic arch, the right, which after passing over the right bronchus turns to the left, at about the level of the body of the third or fourth thoracic vertebra, between the esophagus ventrally and the spinal column dorsally. Either directly dorsal to the esophagus or to its left, the aortic arch joins the descending aorta which usually lies to the left of the midline. The first three branches of the aortic arch are the left common carotid, the right common carotid, and the right subclavian arteries in that order ventrodorsally. The left subclavian artery arises as the fourth branch of the aorta from a diverticulum-like outpouching that lies at the left superior angle of the junction of the right aortic arch with the descending aorta. The diverticulum usually lies against the left side of the esophagus, and into its lower anterior aspect is inserted the superior portion of the ductus arteriosus.

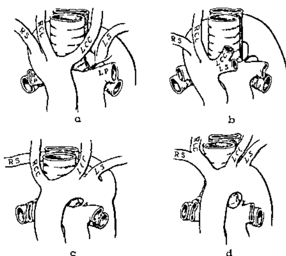


Figure V-92 Vascular rings, subgroup A, continued (From Edwards, 1948b Reproduced by permission of the W B. Saunders Company)

a A right aortic arch with retro-esophageal segment Left descending aorta Left ductus inserts into aortic diverticulum from which left subclavian artery arises

b Right aortic arch with retro-esophageal segment Left descending aorta Left ductus inserts into aortic diverticulum Left subclavian artery originates from left innominate artery

c Right subclavian artery arises as a fourth branch of an otherwise normal aorta

d Normal aorta.

The inferior attachment of the ductus arteriosus is to the left pulmonary artery (Quain, 1844, Turner, 1862; Herringham, 1891, F. C. Abbott, 1892, Reid, 1914, Ewald, 1926, Case 4, Pense, 1930, Bedford and Parkinson, 1936, Herbut, 1943, Case 10)

This condition is comparable with that illustrated in Figure V-91*c* in which there was predicted atresia of that segment of the left aortic arch between the origins of the left common carotid and left subclavian arteries. In that condition, the atretic segment would be identifiable as a fiber-like cord. In the condition under this heading, the atretic segment is no longer identifiable; therefore, on casual examination, one might not identify the anomaly as a variant of the double aortic arch which, however, it should be considered to be. The aortic diverticulum which gives rise to the left subclavian artery and which is a point of attachment for the

ductus arteriosus should be interpreted as a patent posterior portion of a left aortic arch. The segment of the left aortic arch between the origin of the left subclavian and common carotid arteries has disappeared during early embryonic life and is not identifiable

In certain instances, the aortic diverticulum has approximately the same diameter as the subclavian artery to which it gives origin. Under such conditions, the diverticulum appears as the proximal part of the left subclavian artery, and the ductus arteriosus, which actually is attached to the diverticulum, appears to be attached to the beginning of the left subclavian artery (Annan, 1910) Such variations in gross appearance do not alter the basic concepts concerning the significance of the vascular pattern Rather they represent minor variations in relative rates of growth

While there is absence of the symmetrically constricting effects of a continuous double aortic arch, there is, nevertheless, a vascular ring about the trachea in anomalies of this subgroup The ring is formed by the right aortic arch on the right, the retro-esophageal segment of the right aortic arch dorsally, the aortic diverticulum and the ductus arteriosus on the left, and the bifurcation of the pulmonary trunk ventrally. The subclavian artery plays no role in forming the vascular ring In such instances a break in the continuity of the vascular ring may be accomplished by the division of the ductus arteriosus, which allows left lateral expansion of the trachea and the esophagus The procedure also allows the bifurcation of the pulmonary trunk to sag away from the ventral surface of the trachea with relief of pressure against that tube In addition, Gross (1946, 1947) and Gross and Ware (1946), in discussing this type of anomaly, stressed the possibility of compression of the trachea by the left common carotid artery which arises to the right of the midline and crosses ventral to the trachea to achieve its usual position on the left side of the superior mediastinum. They recommended dislocating this vessel from its close association with the trachea if it compresses the air passage unduly.

b *Right-sided aortic arch with retro-esophageal segment and left-sided descending aorta; left subclavian artery originating from left innominate artery.* Referring to the double arch of this subtype (Figure V-91*a*), it is evident that if the portion of the left aortic arch between the origin of the left subclavian artery and the insertion of the ductus arteriosus disappears, the aortic arch pattern appears as in Figure V-92*b*. There is one aortic arch, the right This passes over the right major bronchus, after which it turns to the left and passes between the esophagus and the spinal column, as in the other anomalies previously described. Dorsally, or to the left of the esophagus, it joins the left-sided descending aorta. There is a diverticulum at the junction of the aortic arch and descending aorta (Gruber, 1912, Case 2) The ductus arteriosus is inserted into this diverticulum. The left subclavian artery does not arise from the diverticulum but instead arises from a left-sided innominate artery in common with the left common carotid artery The left innominate artery is the first branch of the aortic arch, the second and third branches being the right common carotid and right subclavian arteries, respectively.

4. Left-sided Aortic Arch and Left-sided Descending Aorta. The types of anomalies that have been considered under Subgroup A thus far were characterized not only by the presence of the ductus arteriosus on the left side but also by the presence of a right-sided aortic arch either alone or associated with a left-sided aortic arch. Since the cephalic part of the descending aorta lay either in the midline or to the left of the midline, the dorsal portion of the right

aortic arch possessed a horizontal segment, posterior to the esophagus, which was directed toward the descending aorta In the remaining types of vascular patterns to be considered in Subgroup A, the left aortic arch is the only one that is present as a continuous functioning vessel. Portions of the right arch have disappeared.

a. *Left-sided aortic arch and left-sided descending aorta, right subclavian artery arising from distal portion of aortic arch or from the descending aorta.* This aortic arch pattern is characterized by the disappearance of the segment of the right portion of the double aortic arch between the origins of the right common carotid and the right subclavian arteries. Consequently, the first branch of an otherwise normal left-sided aortic arch is the right common carotid artery rather than the innominate artery. The second and third branches of the arch are the left common carotid and the left subclavian arteries, respectively. The right subclavian artery arises as the fourth branch of the aorta from either the aortic arch or the cephalic part of the descending aorta (Figure V-92*c*) The origin of this artery is frequently wider than the rest of the intrathoracic portion of the vessel, a feature that is not surprising since the origin of the right subclavian artery in this anomaly represents the most dorsal portion of a right-sided aortic arch From its origin on the left side of the midline, the right subclavian artery proceeds cephalically and to the right in an oblique direction. It crosses the midline usually by passing between the esophagus ventrally, the spinal column dorsally (Thomson, 1893; Holzapfel, 1899; Poynter, 1916, Goldbloom, 1922, Dolgopol, 1934). Less often, as in Bayford's case (1794), the artery lies between the esophagus and the trachea as it passes from the left side of the body to the right side, and even less commonly does it cross ventral to the trachea.

Origin of the right subclavian artery as the fourth branch from an otherwise normal aorta is the one most frequently observed among the anomalies under consideration. It may occur as often as once in every 200 persons. Usually it does not give rise to symptoms. When it does cause symptoms, these are related to interference with the function of the esophagus. While, in the usual case, there are no other malformations associated with this anomaly, Brean and Neuhauser (1947) described this malformation in three infants in association with a patent ductus arteriosus. In only one of these did the right subclavian artery seem to cause dysphagia When the function of the esophagus is compromised by the anomalous artery, the treatment consists of dividing this vessel.

b. *Left-sided aortic arch and left-sided descending aorta; normal arch and branches.* It seems logical to consider the features of the normal aorta at this point since it too can be visualized as a modification of the double aortic arch. If one assumes that the double aortic arch of Subgroup A is modified in such a way that there is loss of the right arch between the origin of the right subclavian artery and the descending aorta, one arrives at the structure of the normal aorta (Figure V-92*d*).

Under these circumstances, the first branch of the aortic arch is the innominate artery, which soon divides into the right common carotid and right subclavian arteries. The second branch is the left common carotid artery and the third is the left subclavian artery. The descending aorta lies on the left side and no undue compression upon the trachea or the esophagus is caused by the aortic arch or its branches. The ductus arteriosus extends from the left pulmonary artery to the aorta at a point beyond the origin of the left subclavian artery.

c. *Interruption of the aortic arch.* In

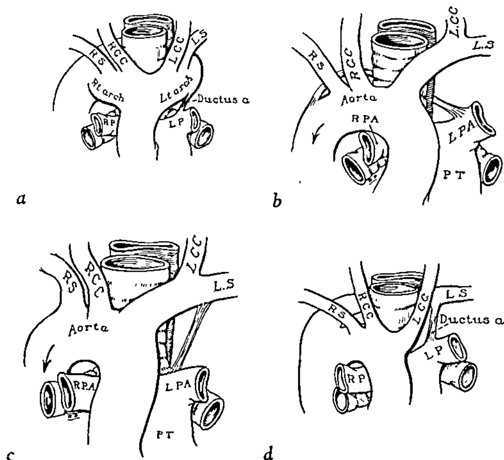


Figure V-93 Vascular rings, subgroup B (Left ductus Right descending aorta) *a* Functioning double aortic arch (From Kirklin and Clagett, 1950)
b Right aortic arch Right descending aorta. Left ductus passing behind esophagus to aorta
c Right aortic arch Right descending aorta Left ductus arteriosus inserts into left subclavian artery which originates from left innominate artery
d Right arch Right descending aorta Left ductus arteriosus inserts into left subclavian artery which arises as the fourth branch of the aorta (From Kirklin and Clagett, 1950)

this form the process of disappearance of elements of the aortic arch system has gone beyond normal bounds Usually the zone of excessive loss of the arch system is in the left arch between the origin of the left subclavian artery and the ductus arteriosus, as in the case of Sewart (1948) Thus the aortic arch is on the left side and after giving off the standard branches, it loses continuity with the rest of the aorta. The descending aorta is supplied by the right ventricle through the medium of a patent ductus arteriosus

In the case of Herzog (1948) the left arch had become interrupted between the left common carotid and the left subclavian arteries The left subclavian artery arose from the cephalic portion of the descending aorta which was supplied through the ductus arteriosus.

Subgroup B: Left-sided Ductus Arteriosus and Right-sided Descending Aorta

In a relatively small number of cases the aortic arch pattern is such that the ductus arteriosus is on the left side and the descending aorta is on the right side. The basic pattern of this subgroup is the functioning double aortic arch, as illustrated in Figure V-93*a*.

1. Functioning Double Aortic Arch. As in the other forms of double aortic arch, an aortic arch passes over each bronchus. The left arch is the one which is retro-esophageal, joining the right arch on the right side of the midline to form the descending aorta. The latter structure is on the right. Each arch gives rise to its respective common carotid and subclavian arteries in that order. The ductus arteriosus is on the left side, running from the left pulmonary artery to the left arch; it inserts into the latter at a point just beyond the origin of the left subclavian artery (Figure V-93*a*).

Cases of this type have been described by Shaw (1897), Herrmann (1928), Herbut and Smith (1943), Kaiser (1948), and by Griswold and Young (1949, Case 2). In Herrmann's patient, a girl aged six months, the ductus arteriosus was patent. In the patient of Griswold and Young the tetralogy of Fallot was associated with the aortic malformation.

2. Partial Atresia of One Arch. The case of Issajew (1931) is an example of double aortic arch of Subgroup B in which there is atresia of one arch. The left arch was atretic between the origins of the left subclavian artery and the left common carotid artery.

3. Right Aortic Arch, Right Descending Aorta and Left-sided Ductus Arteriosus. This pattern of the aortic arch is the most common of those characterized by a left-sided ductus arteriosus and a right-sided descending aorta. In it the aortic arch and the descending aorta are both on the right side. The ductus arteriosus arises from the left pulmonary artery and may insert either into the aorta or into the left subclavian artery.

Three patterns are identifiable depending upon the location of interruption of the left of the double arch illustrated in Figure V-93*a*.

a. *Right arch; right descending aorta; left ductus inserting into the aorta.* If the left side of the double aortic arch of Subgroup B is interrupted between the origin of the left subclavian artery and the insertion of the ductus arteriosus, the pattern illustrated in Figure V-93*b* is obtained. The arch is on the right. Its first branch is a left innominate artery from which the left common carotid and left subclavian arteries arise. The ductus passes dorsal to the esophagus to the right side to insert into the aorta at the junction of the arch with the descending aorta (Ewald, 1926, Case 2, Halpert *et al.*, 1949). This form may be associated with symptoms of tracheal and esophageal compression as emphasized by Neuhauser (1949).

b. *Right arch, right descending aorta; left ductus inserting into left subclavian artery originating from left innominate artery.* In the form described immediately preceding, the left of the double arch of Subgroup B was interrupted between the left subclavian artery and the ductus arteriosus. If the left arch is interrupted dorsal to the insertion of the ductus into it, the pattern illustrated in Figure V-93*c* is obtained. The pattern illustrated in Figure V-93*b* is present with the exception that the ductus inserts into either the left innominate or the left subclavian artery. This is the pattern that may be seen in the tetralogy of Fallot when a right aortic arch exists (Bahnson and Blalock, 1950).

c. *Right arch; right descending aorta, left ductus inserting into left subclavian artery originating as fourth branch of the aorta* (Figure V-93*d*). If the left arch of the double arch of Subgroup B is interrupted between the origins of the left common carotid and left subclavian arteries, the left subclavian artery arises as the fourth branch of the aorta or from a diverticulum of the cephalic part of the descending aorta on the right side of the body and then crosses to the left, dorsal to the esophagus. The ductus arteriosus in-

serts into the base of the left subclavian artery or into the diverticulum from which it arises (Gruber, 1912, Case 1, Biedermann, 1931)

Humphreys (1948) described a case in which the ductus arteriosus was patent, and inserted into the left subclavian artery which arose as the fourth branch of the aorta

The case of Siekert (1949) is probably best classed as belonging in this category In his patient, a woman aged 23 years, with the Eisenmenger complex, a right arch gave rise to the left common carotid, the right common carotid and the right subclavian arteries, proceeding ventrodorsally in the order mentioned The aorta thus proceeded to the midline where it was joined by a vessel which was continuous with a left-sided patent ductus and from which the left subclavian artery arose. Though Siekert claimed that the ductus inserted into the aorta, it is preferable to consider that the posterior portion of the left arch was retained and the ductus inserted into it, and that the left subclavian artery arose from the remnant of the left arch.

4. Left Arch, Left Ductus and Right Descending Aorta. In those malformations of Subgroup B with but one arch, so far considered, the right arch was the one present since part or all of the left arch had become obliterated Were parts of the right arch to disappear while the left arch remained intact, malformations represented by a left arch, a left ductus arteriosus and a right descending aorta would result. Though such malformations are hypothetical possibilities, it seems very unlikely that they would occur

Subgroup C: Right-sided Ductus Arteriosus and Right-sided Descending Aorta

1. Functioning Double Aortic Arch. The basic pattern of Subgroup C is the functioning double aortic arch of this subgroup Though there is no established example of this form of malformation, the second case of Sweet and associates (1947) is suggestive.

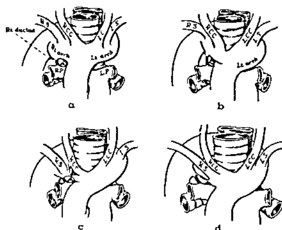


Figure V-94 Vascular rings, subgroup C (Right ductus Right descending aorta) (From Edwards, 1948b Reproduced by permission of the W. B Saunders Company)

a Functioning double aortic arch in which both arches are of about equal size (Hypothetical form)

b Functioning double aortic arch in which the right is the narrower of the two arches (Hypothetical form)

c Double aortic arch with atresia of the right arch between the right common carotid and right subclavian arteries (Hypothetical form)

d Double aortic arch with atresia of right arch between the right subclavian artery and insertion of right ductus arteriosus (Hypothetical form)

No ductus arteriosus was found on either side during operation on this patient Had a right-sided ductus arteriosus been discovered, the criteria for the functioning double aortic arch of Subgroup C would have been fulfilled. Though the existence of this form is still hypothetical, derivatives of it are known and its anatomic characteristics may be defined (Figure V-94*a*).

The ascending aorta bifurcates ventral of the trachea. The left and right arches pass over the respective major bronchi. Since the cephalic part of the descending aorta lies on the right, the left arch crosses to the right dorsal to the esophagus to join with the right arch as the latter blends with the descending aorta. The subclavian and common carotid arteries arise inde-

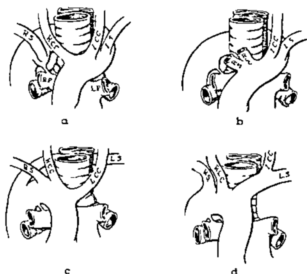


Figure V-95 Vascular rings, subgroup C, continued (From Edwards, 1948b Reproduced by permission of the W B Saunders Company.)

a Left aortic arch with retro-esophageal segment Right descending aorta Right ductus arteriosus inserts into aortic diverticulum from which right subclavian artery arises

b Left aortic arch with retro-esophageal segment Right descending aorta Ductus inserts into aortic diverticulum Right subclavian artery originates from right innominate artery

c Right aortic arch Right descending aorta Left subclavian artery originates as fourth branch of aorta

d Right aortic arch Right descending aorta Left innominate artery

pendently from the respective arches. The ductus runs between the right pulmonary artery and the right arch and is inserted into the latter just distal to the origin of the right subclavian artery. In the hypothetical form illustrated in Figure V-94*a* the two arches are portrayed as being of equal caliber. In Figure V-94*b* is shown a functioning double aortic arch in which the left is the larger of the two. This pattern of the arches is like that in the case of Sweet and associates.

2. Partial Atresia of an Arch. In Subgroup C patterns characterized by partial atresia of one of the two arches have not been described and their existence is hypothetical. In Figure V-94*c* the atresia is shown between the origins of the right common carotid and subclavian arteries; while in Figure V-94*d*, the atresia lies between the right subclavian artery and the right-sided ductus arteriosus. Malformations are known in which the right arch has "dropped out" at locations corresponding to the levels of atresia represented in these two figures. These forms follow.

3. Left-sided Aortic Arch with Retroesophageal Segment and Descending Aorta on Right. a. *Right subclavian artery originating from aortic diverticulum.* If that segment of the right arch represented as atretic in Figure V-94*c* is lost, the following pattern is encountered (Figure V-95*a*).

There is but one continuous arch, the left. After crossing the left major bronchus this arch deviates to the right to pass dorsal to the esophagus and to join the descending aorta on the right side. At the junction of the left arch with the descending aorta there is a diverticulum which represents a remnant of the posterior extremity of the right arch. Into this structure the ductus arteriosus is inserted and the right subclavian artery arises from the diverticulum. The case which I reported (Edwards, 1948a) is representative of this form of anomalous aorta.

b *Right subclavian artery originating from a right-sided innominate artery* (Figure V-95*b*). If the right arch has been interrupted between the origins of the right subclavian and right carotid arteries, the right subclavian artery arises from the aortic diverticulum. If, on the other hand, the right arch disappears posterior to the origin of the subclavian artery, that vessel arises in common with the right common carotid artery from a right-sided innominate artery. The arch is on the left side and after passing over the left bronchus, passes dorsal to the esophagus to join the descending aorta on the right side.

Were a right-sided ductus arteriosus described in each of the two cases of Paul (1948), his cases could be categorized as belonging to this type of malformation.

4. Right-sided Aortic Arch and Descending Aorta on Right Side. If in the basic form of this subgroup (Figure V-94*a*) the right arch remains intact but parts of the left arch disappear, the following forms are achieved.

a *Left subclavian artery originating as fourth branch of the right aortic arch* (Figure V-95*c*) (Lockwood, 1884, Kopsch, 1914; Dittrich, quoted by Renander, 1926) If the left arch is interrupted between the origins of the left common carotid and left subclavian arteries, the left subclavian artery loses its connection with the ventral part of the aorta and arises as the fourth branch of the aorta. It then crosses dorsal to the esophagus from right to left The right-sided ductus inserts into the aortic arch between the origins of the right and left subclavian arteries

b *Left subclavian artery originating from left-sided innominate artery* (Figure V-95*d*) (Epstein, 1886, Reid, 1914, Case 2, Assmann, 1924; Ewald, 1926, Case 1; Sprong and Cutler, 1930) If the left arch should disappear dorsal to the origin of the left subclavian artery, the mirror image of the normal would be achieved There is a right arch, a right descending aorta, and the ductus arteriosus is on the right. There is a left innominate artery. Though this pattern of aortic arch may occur in the absence of a cardiac malformation, it is usually associated with the tetralogy of Fallot. As Bahnson and Blalock have emphasized, when a right arch and right descending aorta are found, the ductus arteriosus need not be on the right side but may be on the left as in Subgroup B.

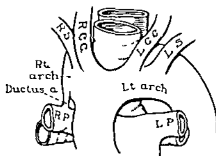


Figure V-96 Vascular rings, subgroup D (Right ductus Left descending aorta) The functioning double aortic arch which is illustrated is a hypothetical form from which other forms may be derived All derivatives are as yet hypothetical (From Kirklin and Clagett, 1950.)

Nevertheless, a right ductus may occur in some of the cases An example of this type of aortic malformation is illustrated in the section on the tetralogy of Fallot as Figures V-26*c* and *d*, page 318.

Subgroup D: Right-sided Ductus Arteriosus and Left-sided Descending Aorta

This subgroup may be considered the mirror image of Subgroup B The basic pattern of Subgroup D is likewise a functioning double aortic arch (Figure V-96). The right arch crosses the midline dorsal to the esophagus. It then joins with the left arch to form the descending aorta which lies on the left. The ductus arteriosus is a right-sided structure, inserting into the right arch posterior to the take-off of the right subclavian artery As far as I am aware, no member of Subgroup D has been reported, but the double arch and derivatives of it remain as hypothetical possibilities.

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Congenital Malformations

H. Malformations of the Thoracic Veins

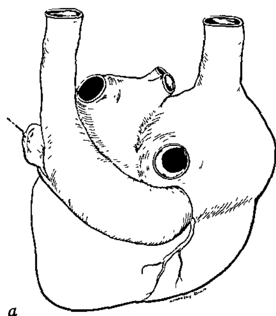
SYSTEMIC VEINS

Persistent Left Superior Vena Cava

With rare exceptions the malformations of the systemic intrathoracic veins cause no functional disturbance The most common of these malformations is persistent left superior vena cava. In this condition the right innominate vein is formed in a normal manner by the union of the right internal jugular and subclavian veins It does not receive the left innominate vein to form the superior vena cava. Instead, it descends in the position of the superior vena cava and, after receiving the azygos vein, enters the right atrium as the superior vena cava does normally On the left side the left innominate vein is formed by its usual tributaries. Instead of crossing to the right, the left innominate vein descends vertically to enter the thorax. In this position it is called left superior vena cava. Here it passes ventrally to the aortic arch and the root of the left lung At the inferior level of the root of the left lung the left superior vena cava turns to the right, pierces the pericardium and reaches the left aspect of the left atrioventricular groove. Here it becomes continuous with the coronary sinus (Figure V-97*a*). The latter, by virtue of carrying the additional blood coming to it by the anomalous connection, is wider than normal. The coronary sinus terminates in the right atrium. Therefore, though the course of blood from the left arm and left side of the head and neck is abnormal, the blood ends, as normally, in the right atrium (Chaffey, 1885).

The papers of Halpert and Coman (1930) and of Atwell and Zoltowski (1938) contain extensive bibliographies on malformations of the superior vena cava A variation of the usual pattern of persistent left superior vena cava was observed in the cases of Hepburn (1887) and Papez (1938). In these cases, as in others mentioned in the bibliographies of these authors, there was the usual pattern of a persistent left superior vena cava as well as a vessel which connected the two innominate veins in the lower cervical region.

A step beyond this stage was exhibited by the cases of Greenfield (1876), of Halpert and Coman (1930) and Atwell and Zoltowski (1938). In these there was *absence of the right superior vena cava.* In the neck the venous system was essentially a mirror image of the normal. The right innominate vein crossed to the left and joined the left innominate vein to form a



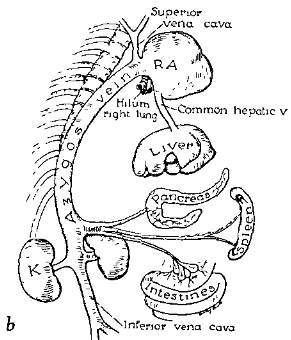


Figure V-97 *a* Persistent left superior vena cava Posterior view of heart showing continuity of persistent left superior vena cava with the dilated coronary sinus

b, Union of the inferior vena cava with the azygos vein Absence of the portal vein The splanchnic veins drain into the abdominal systemic vein A common hepatic vein runs from the liver to the right atrium (From a case reported by Hickman and associates [1949], occurring in a dog Reproduced by permission of the Wistar Institute, publishers of Anatomical Record)

left superior vena cava The latter then followed the usual course of a left superior vena cava and terminated in the coronary sinus.

The association of a persistent left superior vena cava with atresia of the right atrial ostium of the coronary sinus is discussed under Malformations of the Coronary Vessels

The superior vena caval system may be anomalous not only in its configuration but also with respect to connections with other structures In Nabarro's (1903) Case 2 a left hepatic vein joined the left side of the coronary sinus near the termination of a persistent left superior vena cava.

The termination of a pulmonary vein in the coronary sinus or in the caval system is discussed in the section dealing with anomalous drainage of the pulmonary veins.

In rare instances a persistent left superior vena cava, after passing ventral to the root of the left lung, terminates in the left atrium instead of ending in the coronary sinus In this way venous blood is carried directly to the left side of the heart (MacKenzie, 1880, Hu, 1929, Potter, 1948, Case 3) This anomalous connection should not be confused with the unusual venous connections between the left atrium and the superior caval system in which the anomalous vein lies dorsal to the left bronchus and left pulmonary artery. Connections of the latter type may be called "levoatriocardinal veins" These will be discussed with the pulmonary veins

Putschar (1938) described a case in which the *umbilical vein* by-passed the portal system and *entered the right atrium.*

Continuity of Azygos Vein and Inferior Vena Cava

In rare instances the inferior vena cava, after receiving the renal veins, fails to

follow its usual course Instead it becomes continuous with the lower portion of the azygos vein (Griffith, 1891, Miller, 1925). By virtue of the fact that the azygos vein carries the additional blood brought to it by the inferior vena cava, it becomes greatly dilated No functional disturbance results since the venous blood from the lower part of the body is carried to the right atrium Emerging from the liver in the usual location of the terminal portion of the inferior vena cava is a narrow vein representing a common hepatic vein.

In a dog with venous abnormalities as outlined, Hickman and associates (1949) (Figure V-97*b*) found an additional abnormality. There was *absence of the portal vein.* In this case the veins from the splanchnic area converged to join the abdominal systemic vein at the level at which the inferior vena cava and azygos vein blended. These authors referred to two cases of *absence of the portal vein in human subjects.* The case of Abernethy (1793) was essentially like that described in Hickman's dog. The case of Wilson, that of a girl aged 13 years who died accidentally, was described by Kiernan (1833). In this case, absence of the portal vein was evidently associated with a normally disposed inferior vena cava.

PULMONARY VEINS

Anomalous Drainage

One or all of the pulmonary veins may drain anomalously into the right atrium directly (Graham, 1944) or into one of its tributary veins

These veins are the superior vena cava (Hepburn, 1887, MacCready, 1918, Case 3, Hughes and Rumore, 1944, Case 1, Conn *et al.*, 1942, Smith, 1951), the azygos vein, the left innominate vein (Chaffey, 1885, MacCready, 1918, Cases 1 and 2, Dean and Fox, 1928; Hughes and Rumore, Case 2, Conant and Kurland, 1947), the left subclavian vein (Ramsbotham, 1829), the coronary sinus (Nabarro, 1903, Case 1; DeGroat and Thatcher, 1936), the inferior vena cava, the ductus venosus (Ghon, 1916; Mehn and Hirsch, 1947; Edwards and DuShane, 1950) (Figure V-98), the portal vein (Ramsbotham, Young, 1947, Mykschowszky, 1948, Weinberg and Kolson, 1949) (Figure V-99), or a gastric vein (Hu, 1929).

It is important to distinguish those cases in which the anomalous drainage is partial from those in which it is complete. This is stressed because partial anomalous drainage of the pulmonary veins functions differently from complete anomalous drainage of the pulmonary veins; the former functionally resembles atrial septal defect while the latter, in some ways, acts as though a two-chambered heart were present.

Brody (1942) found the commonest termination of anomalous drainage of pulmonary vein to be the superior vena cava, followed in decreasing order of frequency by the right atrium, the left innominate vein, the coronary sinus, azygos vein, inferior vena cava and the left subclavian vein. The veins of the portal system are less frequent sites for insertion of pulmonary veins.

Anomalous veins of the right lung tend to drain into the superior vena cava or the right atrium, while those of the left lung tend to drain into the left innominate vein. Anomalous drainage may involve one or several lobes. The upper lobe of the right lung is the one most commonly involved in partial anomalous drainage of the pulmonary veins Usually when complete anomalous drainage occurs, the veins from all of the pulmonary lobes converge to form a

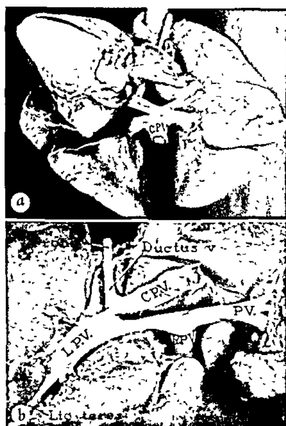


Figure V-98 Complete anomalous pulmonary venous drainage into the ductus venosus The second patient of Edwards and DuShane, a male infant six days old (Reproduced by permission of *Archives of Pathology*)

a Ventral view of the lungs The heart has been displaced to the right A common pulmonary vein (*C P V*) is formed by union of four pulmonary veins The common vein lay ventral to the esophagus and descended through the diaphragm into the abdomen

b The common pulmonary vein (*C P V*) inserts into the narrow ductus venosus (Ductus v) *P V*, portal vein, *R P V*, right portal vein, *L P V*, left portal vein

single common pulmonary vein which in turn *inserts* anomalously (Figure V-98*a*) In Ramsbotham's case there was complete anomalous drainage of an unusual type in that a part of the drainage was into the left subclavian vein and part into the portal vein. Anomalous drainage of the pulmonary veins may occur in association with other cardiovascular malformations or it may occur independently The latter is somewhat commoner than the former

In Kernan's case (1944) an anomalous pulmonary vein caused symptoms from *compression of a bronchus.*

Reports on anomalous drainage of the pulmonary veins are uncommon. In 1942 Brody made a classic review of 106 cases in which necropsy had been performed and in which there was complete or partial drainage of the pulmonary veins into the right atrium or into one of its tributaries. The report included 4 cases which he had observed personally and 102 which had been reported by others. In this collection of cases there were 68 in which the anomalous drainage was partial and 38 in which it was complete

In 1947 Young collected data on certain reported cases of anomalous pulmonary venous drainage which Brody had not mentioned These included several reported since the time of Brody's paper. Young's collection brought the total number of reported instances of anomalous drainage of the pulmonary veins up to 127. Young added a case of his own in his report If to this figure is added the case of Hu, reported in 1929, and mentioned by Mehn and Hirsch but not by Brody or Young, as well as the cases of Mehn and Hirsch, of Mykschowszky, of Graham, of Kernan (1944), of Weinberg and Kolson, and of Edwards and DuShane, the total number of cases of anomalous pulmonary venous drainage in which necropsy was performed would be 134.

Doubtless there are many other cases studied pathologically which have not come to light because of the fact that the titles of papers reporting these anomalies do not suggest the presence of anomalous pulmonary veins. For example the patient of Feldman and Chalmers (1933) is a case in point. Their patient had complete transposition of the great vessels. In addition, all of the pulmonary veins drained into the right atrium This case is not mentioned in existing reviews on pulmonary venous anomalies. Moreover, we believe that

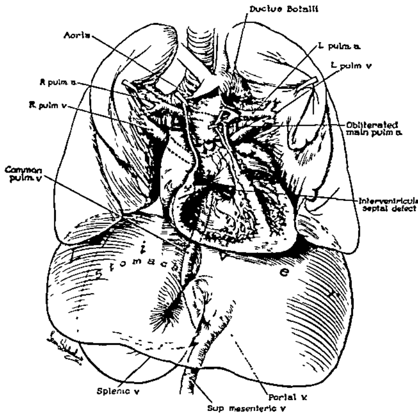


Figure V-99 Complete drainage of the pulmonary veins into the portal vein in the case of Weinberg and Kolson (1949). In this patient, a male infant aged six days, there was inversion of the abdominal viscera as well as isolated levocardia and atresia of the pulmonary trunk (Reproduced by permission of Dr Weinberg and *Journal of Technical Methods*)

necropsy, unless dissection of the thoracic organs is done in one block, the chance of a pathologist finding anomalous pulmonary veins is practically negligible Therefore, if at necropsy the organs are removed separately, as is the practice of many pathologists, it is likely that many of these malformations will not be discovered. Instances of anomalous pulmonary veins discovered at operation (Brantigan, 1947) or upon clinical investigation (Johnson and McRae, 1948; Dotter *et al.*, 1949; Grishman *et al*, 1949, Knutson *et al*, 1950) have also been reported.

Partial Anomalous Drainage. The effect upon the heart of partial anomalous drainage of the pulmonary veins is like that of atrial septal defect. This includes dilatation of the right atrium and dilatation and hypertrophy of the right ventricle. The pulmonary trunk and the other pulmonary vessels may be dilated. These features may be demonstrated roentgenographically.

In rare instances, as in two of the cases of Grishman and associates (1949), the anomalous vein itself may cast a shadow in the roentgenogram. The clinical diagnosis of partial anomalous drainage of the pulmonary veins is difficult or impossible to make without special studies On cardiac catheterization the right atrial blood has an abnormally high content of oxygen. This condition may of course be the result of an atrial septal defect without other malformations.

If the catheter is passed directly into an anomalous vein, and it is demonstrated that the blood is completely saturated with oxygen, the findings can be considered diagnostic for anomalous drainage of a pulmonary vein (Knutson *et al*, 1950). Even under these circumstances it may be

impossible to rule out an atrial septal defect which may occur in association with partial anomalous drainage of the pulmonary veins (Cournand *et al.*, 1949)

An important distinguishing feature between the functional effects of atrial septal defect and partial anomalous drainage of the pulmonary veins is that in atrial septal defect there may be minor degrees of desaturation of the systemic arterial blood while in partial anomalous drainage of the pulmonary veins under conditions of health, there is no basis for desaturation of the arterial blood. It is to be emphasized, however, that when the two malformations are associated there may be desaturation of the arterial blood on the basis of minor shunting of venous blood across the atrial septal defect into the left atrium According to Brody the patient with partial anomalous drainage of the pulmonary veins may reach adult life Disability is not likely to occur unless more than 50 per cent of the blood which leaves the lungs enters the right side of the heart

Complete Anomalous Drainage. While the patient with partial anomalous drainage of the pulmonary veins does not show cyanosis, has little disability and often reaches adult life, the patient with complete anomalous drainage shows desaturation of the peripheral arterial blood, may be cyanotic and usually dies during early infancy. Not only are the clinical features different but the heart has a different appearance In this malformation, no veins enter the left atrium. The chamber is small and there is always an atrial septal defect This usually takes the form of the type of patency of the foramen ovale seen in the fetus Indeed this is the only channel by which the left atrium receives blood The left ventricle is smaller than normal and much smaller than the right ventricle, which characteristically is dilated and hypertrophied

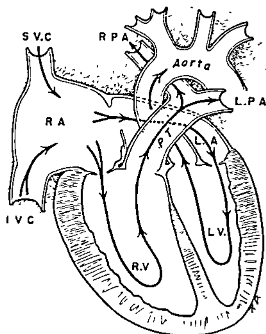


Figure V-100. The intracardiac circulation in complete anomalous drainage of the pulmonary veins (From Edwards and DuShane, 1950 Reproduced by permission of *Archives of Pathology*)

The changes outlined represent secondary effects of the altered circulation of this condition (Figure V-100). The right atrium receives all of the blood, both systemic and pulmonary, which returns to the heart. From this chamber the mixture flows partly through the tricuspid valve to the right ventricle for distribution to the lungs while the remainder flows through the patent foramen ovale into the left atrium. From the latter chamber the mixture flows to the left ventricle and to the systemic circulation. It is obvious, on the basis of mixture of venous and oxygenated blood in the right atrium, that in complete anomalous drainage of the pulmonary veins both an arteriovenous shunt and a venous-arterial shunt exist. The latter is responsible for desaturation of the systemic arterial blood.

It is to be emphasized that the degree of desaturation of the systemic blood will depend upon the relative amount of the right atrial blood which passes throu

the foramen ovale as compared with that which passes through the tricuspid valve Several factors influence the distribution of the right atrial blood. Important ones are the size of the foramen ovale and the capacity of the right ventricle to fill All other factors being equal, the smaller the foramen ovale the less will be the distribution of the mixture of blood to the left atrium and by the same token, the greater will be the flow through the tricuspid valve Within certain limits, the patient with the smaller foramen ovale has an advantage over the patient with the larger foramen, since the greater the pulmonary blood flow the greater will be the content of oxygen in the blood of the right atrium and concomitantly the higher will be the oxygen content of the blood in the systemic arterial circulation. Of course, when the foramen ovale is sufficiently reduced in size to cause insufficient flow of blood across it, the higher oxygen content in the mixture will be of little value to the patient because of the concomitant inadequate systemic blood flow

The right ventricle may not fill adequately because of failure. This may result from the burden of carrying excessive volumes of blood. Another factor is the possible occurrence of impaired venous return from the lungs. This results either from stenosis of the anomalous pulmonary veins or from increased resistance to flow incident to the interposition of the hepatic sinusoids between the pulmonary veins and the right atrium. This is pertinent to those cases in which the anomalous drainage is into the portal vein. In these cases the blood which flows from the lungs must traverse the hepatic sinusoids before returning to the heart. The resistance to flow imparted by the hepatic sinusoids may create a sufficient barrier to pulmonary venous drainage to cause right ventricular failure.

Whatever the cause of right ventricular failure, when it occurs it may be easier for the mixed blood in the right atrium to flow across the foramen ovale than through the tricuspid valve. When this happens there is diminished pulmonary blood flow and the mixed blood in the right atrium contains less oxygen than before right ventricular failure had made its appearance. Cyanosis may increase in degree.

Levoatrio-cardinal Vein

There are at least three established examples of communication between the left atrium and a systemic vein other than connections of a left superior vena cava or the coronary sinus with the left atrium (McIntosh, 1926, Harris *et al.*, 1927, Edwards and DuShane, 1950). The anomalous vessel arises from the dorsal aspect of the left atrium near the entrance of one of the pulmonary veins. It then ascends dorsal to the bronchus and the pulmonary artery of the side on which it originates.

In McIntosh's case the systemic vein that connected with the anomalous vessel was the superior vena cava, in Harris' case the right internal jugular vein, and in the case of Edwards and DuShane the left innominate vein (Figure V-52*b*). Since each of the systemic veins into which the anomalous vessel inserts is a derivative of the cardinal system, the name "levoatrio-cardinal vein" has been suggested for this structure.

The *developmental basis for a levoatrio-cardinal vein* seems intimately associated with the development of the pulmonary veins (Figure V-101). In Chapter II it is related that the primordia of the pulmonary veins are represented as a capillary plexus about the lung buds. These ultimately coalesce to give rise to one vein for each pulmonary lobe. Each of these veins is tributary to a common pulmonary vein which in turn is connected with the left atrium. By a process of differential growth the common pulmonary vein and its tribu-

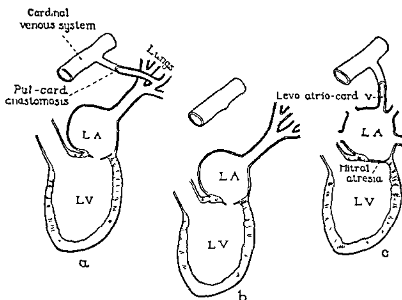


Figure V-101 The developmental basis for formation of a levoatrio-cardinal vein In *a* is shown a communication between a pulmonary vein and a representative of the cardinal venous system This is normal at an early stage of development Later, as represented in *b*, the communication disappears If it is retained, the communication is carried into the dorsal wall of the left atrium along with the pulmonary vein to which it is attached (see *c*) (From Edwards and DuShane, 1950 Reproduced by permission of *Archives of Pathology*)

taries become incorporated into the dorsal wall of the left atrium As the process of blending of the pulmonary venous system with the left atrial wall proceeds, the tributaries of the common pulmonary vein become absorbed into the wall of the left atrium. In this way there results the adult condition of four pulmonary veins joining the left atrium independently

In the early stages of the formation of the pulmonary veins, there are connections between the pulmonary venous primordia on one hand and the elements of the cardinal veins and the esophageal veins on the other. Normally these connections are interrupted If one of these to a cardinal vein is retained, the connection is carried into the wall of the left atrium along with the pulmonary vein to which it is attached. This results in the gross anatomic feature of a vein connecting the left atrium with a derivative of the cardinal system.

In the cases of McIntosh and of Edwards and DuShane the levoatrio-cardinal vein was of functional significance in that in each of these cases there was mitral atresia and premature closure of the foramen ovale The levoatrio-cardinal vein represented the only effective outlet for blood coming to the left atrium from the lungs. In Harris' case there was complete transposition of the great vessels The anomalous venous channel was probably of some beneficial influence as an additional communication between the two circulations

Stenosis or Atresia of Common Pulmonary Vein (Cor Triatriatum)

There is a rare and interesting condition in which the pulmonary veins enter an accessory chamber which lies attached to the dorsal aspect of the left atrium

Loeffler (1949) divided the cases into three groups. In one there is no communication between the accessory chamber and the left atrium. Connection between the accessory chamber and the right atrium or partial anomalous drainage of some of the

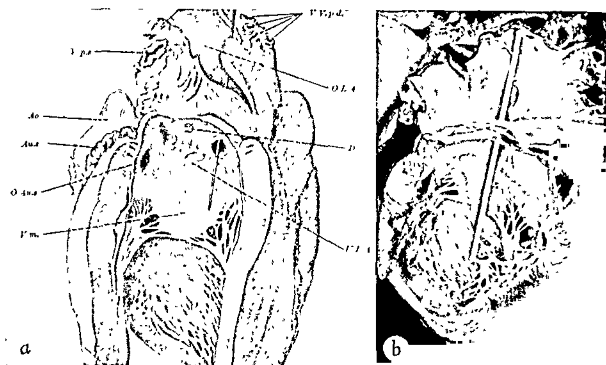


Figure V-102 *a* Congenital stenosis of the common pulmonary vein (the case of Borst) An accessory chamber representing a dilated common pulmonary vein receives the four pulmonary veins and communicates by way of a narrow opening with the left atrial chamber

b Stenosis of the common pulmonary vein in a female infant aged seven and one-half months This specimen in the Mayo Clinic pathologic collection is virtually identical with that of Borst, illustrated in *a*

pulmonary veins may exist. These patients usually die in infancy

In the second group one or several small openings of only a few millimeters' width exist between the floor of the accessory chamber and the roof of the left atrium Except for Borst's patient (1905), who lived 38 years, patients with this type of malformation die in infancy.

The third group is characterized by a relatively wide connection between the accessory chamber and the left atrium. The patients usually live to adult life Griffith's (1903) and Loeffler's patients represent this type. Loeffler's patient was 70 years old.

The two chambers, the one which receives the pulmonary veins and the one caudal to it, taken together present the appearance of a left atrium and an accessory left atrium (Figure V-102). The chamber that lies caudal connects with the auricular appendage and, by way of a normal mitral valve, with the left ventricle. The appearance of two left atria is responsible for application of the name "cor triatriatum" to this condition. The "accessory" atrium is to be considered a common pulmonary vein which has failed to become incorporated into the dorsal wall of the left atrium, as happens in the normal embryo (Figure V-103). The narrow opening between the left atrium and the "accessory atrium" probably represents the original point of junction between the left atrium and the common pulmonary vein of the embryo. The group with no connection between the accessory chamber and the left atrium represents either failure of union of the common pulmonary vein with the left atrium or secondary closure of the ostium.

Functionally, stenosis of the common pulmonary vein is similar to mitral stenosis

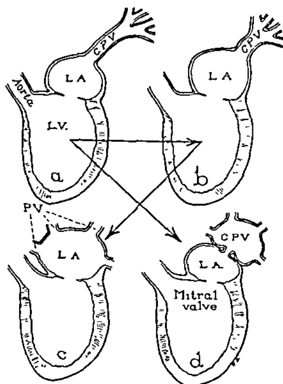


Figure V-103 Diagrammatic representation of the

pulmonary vein

in that it represents a barrier to pulmonary venous drainage

In the one example of this condition in the Mayo Clinic pathologic collection (Figure V-102*b*), which was from a female infant 7½ months old, there were right ventricular hypertrophy and pulmonary vascular changes resembling those seen in acquired mitral stenosis Similar secondary effects of impaired venous return are present in the heart with this condition in the collection of the Registry of Cardiovascular Pathology at the Armed Forces Institute of Pathology The latter heart was from an infant about 20 months of age

A feature dissimilar from mitral stenosis is that the mitral valve is normally formed and so mitral insufficiency is not present. On hypothetical grounds the patient with congenital stenosis of the common pulmonary vein should exhibit the same clinical features as the patient with mitral stenosis, including a presystolic murmur but with the exception that a systolic murmur of associated mitral insufficiency should not be present in congenital pulmonary venous stenosis This was the case in the patient of Borst

Pulmonary Arteriovenous Fistula

Congenital pulmonary arteriovenous fistula, variously called *arteriovenous aneurysm* and *cavernous hemangioma of the lung*, is usually confined to one pulmonary lobe. In the patient of Sisson and associates (1945), on whom necropsy was performed, there were fistulas in both lungs. Part or all of the lobe is replaced by a plexus of various-sized and tortuous vessels which intercommunicate. The importance of the condition is that it allows pulmonary arterial blood to pass to the pulmonary veins and so to the left side of the heart without oxygenation in the lungs As a result, there may be visible cyanosis and the other attendant features of hypoxia including weakness, fainting, polycythemia and clubbing of the fingers and the toes (Goldman, 1943) It was believed for many years that some of the patients had had severe cardiac malformations (Baer *et al*, 1950). Studies in recent years have demonstrated that the lesion may be visualized on roentgenographic examination (Smith and Horton, 1939, Makler and Zion, 1946, Grishman *et al*, 1949), and cure may be effected by resection of the involved pulmonary lobe (Hepburn and Dauphinee, 1942, Jones and Thompson, 1944, Burchell and Clagett, 1947; Maier *et al*, 1948, Wodehouse, 1948) or of the individual lesions when they are multiple (Janes, 1944).

Since the blood which flows through th

anomalous communication is venous blood which by-passes normal pulmonary tissue, it is to be anticipated that cerebral abscess may develop as a complication of congenital pulmonary arteriovenous fistula, as it may in those types of congenital cardiac disease which are characterized by venous-arterial shunts.

Indeed, such a complication has been reported by Wodehouse in a boy aged 13 years with a pulmonary arteriovenous fistula. Necropsy revealed no intravascular focus of infection. This occurrence is consistent with the condition in which cerebral abscess complicates a cardiac malformation.

Bacterial infection of the fistula is another complication which might be anticipated. This has been described by Maier and associates. The patient was a woman aged 20 years who was cured both of the fistula and of the infection by excision of the involved lobe.

A peculiar association of telangiectasia has been noted as frequent in patients with congenital arteriovenous fistula of the lung. In some of the cases with the pulmonary malformation there is a tendency toward familial telangiectasia (Goldman, 1948, Armentrout and Underwood, 1950).

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CHAPTER VI

Degenerative Diseases

WILLIAM B. WARTMAN
and
WILLARD T. HILL

POSTMORTEM CHANGES

ACCORDING TO Aschoff (1919), rigor mortis involves the heart earlier than the skeletal muscle, starting within one hour after death. The left ventricle is the first portion of the heart to be involved. Aschoff believed this to be the reason why the left ventricle, after death, contains practically no blood while the right ventricle is still partly filled. Most of the liquid blood is found in the right atrium. In some hearts with severe degenerative changes of the myocardium, rigor mortis does not occur. After 12 to 24 hours, rigor mortis disappears and the consistency of the heart becomes very soft, the myocardium becomes more and more parboiled in appearance, its normal architecture increasingly obscured, and the papillary muscles and

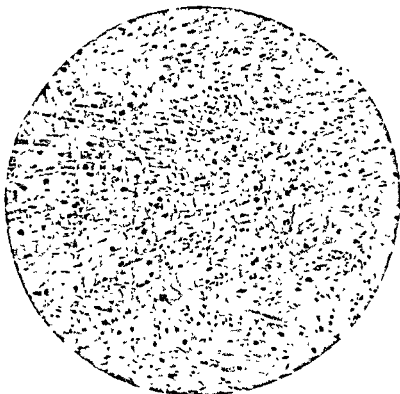


Figure VI-1 Segmentation of cardiac muscle fibers Death was caused by lobar pneumonia Autopsy was performed 70 hours after death (WCGH, 42 A 54)

columnae carneae flattened About 24 hours after death, and sooner if the body is not refrigerated, the endocardium becomes gradually stained with decomposed hemoglobin and assumes a red color This is particularly noticeable in the valvular endocardium. Later, the hemoglobin becomes similarly diffused into the myocardium and pericardium When putrefaction occurs, bubbles of gas may be found in the cardiac chambers, particularly in the right atrium.

Compared to thrombi, clots are soft The latter are either dark red or yellowish white

are commonly found in the atria, and especially within the auricular appendages and in the apical portion of the ventricles. They may be attached by strands between the pectinate muscles of the auricular appendages. Clots are easily removed with forceps or by a stream of water. They also often extend into the great vessels or from one cavity into an adjacent cavity Characteristically they are smooth and elastic

Thrombi are drier than clots, are not elastic and are easily torn when an attempt is made to remove them They are not as smooth and glistening as clots, and are attached to the underlying endocardium

Segmentation and Fragmentation of Myocardium

Segmentation is usually described as separation of the myocardial muscle fibers in the line of the intercalated discs (Figure VI-1) and fragmentation as fracture of the fibers at some point between the discs

tinct conditions sometimes occurring during life, and considered them to be a caus

of death. (See Hektoen, 1897, and Saphir and Karsner, 1924, for older literature.) They believed that if the ruptured ends of the muscle fibers were straight, it signified that the rupture occurred in the line of the intercalated disc. This process was called segmentation. However, if the ruptured ends were irregular or combshaped (pectinate) it was thought that the line of fracture went through the myocardial fibers between the discs. This process was called fragmentation Jordan and Bardin (1913) found that the intercalated discs in hypertrophic hearts were not arranged as straight lines but were irregular and shaped like the teeth of a comb. It then became clear that segmentation (separation of fibers with straight intercalated discs) and what has often been called fragmentation (separation of fibers with pectinate appearance of discs) are essentially the same process (Saphir and Karsner, 1924). In experiments designed to produce severe dilatation of the heart, Saphir and Karsner showed that prior to rupture of the myocardial fibers, the intercalated discs appeared to be prominent While they considered the results of such experiments to be highly suggestive, they were not ready to apply the findings to human material. It also seems likely that fracture of muscle fibers which is definitely not in relation to the intercalated discs must be considered as an artefact caused by the microtome knife. In such instances it can often be demonstrated that the lines of fracture also pass through the muscle nuclei. Hamperl (1929) believed that fragmentation in the human heart does not occur before onset of rigor mortis and that the points of rupture have some sort of relationship to more severely contracted muscle fibers. He was unable to produce fragmentation in the experimental animal. However, he did not mention the state of the intercalated discs or the relationship between the intercalated discs and the points of rupture.

Saphir (1933) paid special attention to the intercalated discs in human hearts. While in sections of non-dilated hearts, stained with hematoxylin and eosin, the intercalated discs were hardly noticeable, in sections of dilated hearts they were prominent and easily discernible. They were more pronounced in the muscle fibers situated close to the endocardium than in those close to the epicardium. The presence of dilatation of the heart was often indicated by the microscopic appearance of prominent intercalated discs, and this deduction was often confirmed by reference to the gross description of flattened papillary muscles and columnae carneae

DISTURBANCES OF METABOLISM

Disturbances of Protein Metabolism

In certain diseases the intracellular proteins may undergo qualitative or quantitative changes, or abnormal proteins may appear in tissue spaces. In the heart such conditions include cloudy swelling, hydropic degeneration, hyaline degeneration and amyloidosis.

Cloudy Swelling and Hydropic Degeneration. Cloudy swelling is of frequent occurrence and affects particularly the heart, liver and kidneys. The heart may show little change on gross examination, it may at most be slightly enlarged with opaque and granular cut surfaces, an appearance which is described as parboiled. Microscopically the cells are swollen and the cytoplasm is granular and indistinct. Frequently the nucleus is partly obscured. In hydropic degeneration small droplets accumulate in the cytoplasm.



Figure VI-2. Hydropic degeneration of myocardium in heat stroke Death 96 hours after onset of illness X 240 (Courtesy, Armed Forces Institute of Pathology, Acc 95093, Neg 88408)

In hydropic degeneration (Figures VI-2 and VI-3) small acidophilic droplets appear in the sarcoplasm of the muscle fibers Grossly this condition is indistinguishable from cloudy swelling. The nature of the changes in cloudy swelling and hydropic degeneration is not clear and probably is not the same in all cases. The swelling is attributed to increased imbibition of water resulting from a change in osmotic pressure, so that the cells hold more fluid within the sarcoplasm The granules in the sarcoplasm are presumably protein in nature

Lucké and McCutcheon (1926) have shown experimentally that two types of cellular swelling may occur in the eggs of the sea urchin The first type of swelling occurs when the osmotic pressure of the outside solution is lowered Such swelling is reversible; when the cause is removed, the cells return to normal. The second type of swelling is induced by various injurious agents such as acid, ether and heat. This type of swelling is irreversible and the cells are killed. These experiments indicate that there are two types of swelling, one kind occurring in living cells and another occurring in dying or dead cells It is not known whether these results are applicable to human beings, but they suggest that cloudy swelling may not always be reversible and that sometimes it may be associated with death of the cells

Hyaline Degeneration. The recognition of hyaline degeneration cannot be made grossly but must await microscopic analysis. It is seldom diffuse but often localized. It may appear in the form of small acidophilic droplets within the sarcoplasm of the muscle fibers or, when diffuse, replace the muscle fibers. It is probable that this represents coagulation of sarcoplasmic protein which occurs as the fiber dies. An interesting change sometimes occurs in older myocardial infarcts in which dead muscle



Figure VI-3 Hydropic degeneration of myocardium. Same case as that of Figure VI-2 (Courtesy, Armed Forces Institute of Pathology, Acc 95093-2, Neg 88410.)

fibers are not replaced by scar tissue but gradually become hyalinized One may encounter areas in the myocardium which at first glance appear to be normal, in which the muscle fibers show increased eosinophilic staining and have no nuclei. Since the general shape of these fibers is preserved, the term "mummification" may be used for this type of hyalinization.

Whether Zenker's (waxy) degeneration occurs in the myocardium is questionable.

Amyloidosis. This is a condition in which an abnormal protein or protein complex called *amyloid* is deposited in certain tissues of the body. For convenience of discussion, amyloidosis is usually classified as (1) primary; (2) secondary; (3) amyloidosis associated with multiple myeloma; and (4) localized amyloidosis of the heart, larynx, skin, bladder or other organ The most common form is secondary amyloidosis which is ordinarily preceded by chronic suppurative disease or less frequently by nonsuppurative chronic inflammation. Primary amyloidosis and localized amyloidosis occur spontaneously without known cause.

Primary Amyloidosis of the Heart. *Criteria for diagnosis.* The criteria for the diagnosis of primary amyloidosis are given by Hartney and associates (1949). In the order of importance, they are (1) absence of a predisposing factor such as chronic suppuration; (2) failure of the amyloid deposits to show the usual staining reactions for amyloid (the response to dilute

Lugol's solution and sulfuric acid, congo red and crystal violet may be irregular and capricious in primary amyloidosis); (3) non-involvement of organs commonly affected in secondary amyloidosis; and (4) deposits in unusual sites such as the heart, blood vessels, skin and skeletal muscle.

Incidence. Primary amyloidosis is frequently accompanied by cardiac involvement. Lindsay (1946) studied 43 cases at autopsy. Cardiac involvement was present in 39, in 32 of which clinical signs of heart failure were evident during life.

Sites of involvement. The pericardium and epicardium are frequently involved in amyloidosis, the involvement being either nodular or diffuse In the nodular form the deposits vary from one millimeter to several centimeters and may be few or many. The nodules are usually pearly gray and translucent, and occasionally yellowish gray Sometimes the deposits form furrows. In the diffuse type of amyloidosis the epicardium and pericardium are thick, grayish yellow and semitranslucent. Rarely there is a grayish gold, gelatinous membrane on the surface. Microscopically the blood vessels of the pericardium, as well as of the interstitial tissues, are involved. Often rings of amyloid surround the fat cells of the pericardium.

The myocardium is attacked more frequently than other parts of the heart. Both the atria and the ventricles may be either diffusely or focally affected. In diffuse involvement the atrial and ventricular walls are likely to be thick and leathery. Usually they are firm and pale grayish tan or brown and have a waxy, translucent, homogeneous appearance. The muscle cuts with increased resistance and, on opening the heart, the chambers do not collapse but retain their globular shape. Irregular translucent, pearly gray streaks or flecks may be scattered diffusely through the myocardium. In the nodular form the nodules vary from a few millimeters to 4 cm. in diameter and are particularly common in the ventricular wall. Microscopically there are two types of involvement, both of which follow a characteristic pattern. In the first type amyloid is found in blood vessels, including the main coronary arteries, arterioles, capillaries and veins. In the second type there is diffuse interstitial infiltration of the myocardium. The myocardial fibers are compressed and undergo necrosis and atrophy, which may be extensive. When atrophy is present the sarcoplasm is vacuolated and contains deposits of lipid or pigment, and nuclear degeneration and necrosis are common. With excessive deposition, the muscle cells disappear entirely, leaving empty amyloid rings or solid sheets of amyloid. Fragmentation of myocardial fibers is frequent

The mural endocardium is infiltrated in a majority of the recorded cases, usually in the form of stratified or nodular deposits. Occasionally the infiltration is continuous with the amyloid in the myocardium

In 16 of 43 cases of primary systemic amyloidosis reported by Lindsay (1946) amyloid deposits were present in the heart valves. The valvular involvement is usually slight and may only be demonstrable in microscopic sections. A few cases, however, have discrete nodules on the valves measuring from 1 to 3 mm. The amyloid occurs in either the cusp or the annulus of the valve. Sometimes the involvement is diffuse, leading to stiff thick cusps and stenotic orifices. In still other cases the thickening is plaque-like, and occasionally very large nodules are found. All four valves are reported to be involved with about equal frequency. Frequently the amyloid extends from the ring of the valve to its free edge. Amyloid may also lie in the deeper layers of the valvular and mural endocardium.

The chordae tendineae may be involved in the amyloid infiltration. Usually t

amyloid originates in the valvular endocardium and extends into the substance of the chordae tendineae.

The coronary arteries may be so extensively involved as to produce occlusion. Although the large coronary arteries may be affected, it is more usual to find the medium-sized and small arteries involved. The arterioles, capillaries and veins have also been reported as sites of amyloid infiltration.

Clinical manifestations Signs of cardiac insufficiency constitute the most important clinical feature of primary amyloidosis The failure may be produced in a variety of ways. Deposits may form in the valves of the heart and cause stenosis or insufficiency. The material may infiltrate the interstitial tissues of the myocardium, endocardium or pericardium When the coronary arteries are affected, stenosis or occlusion may result with consequent angina pectoris or myocardial infarction It is also recognized that extensive deposits of amyloid in the vessels and alveolar walls of the lungs may lead to hypertrophy of the heart, especially of the right ventricle and atrium. Electrocardiographic findings are variable and include low voltage of the QRS complexes and flattening or inversion of T waves.

Secondary Amyloidosis of the Heart. The heart is usually spared in secondary amyloidosis. However, in exceptional cases small deposits of amyloid may be found. Thus, Huebschmann (1907) reported that in eight of nine consecutive autopsies on tuberculous patients with amyloidosis, the amyloid was found in the heart also. Usually it is located in blood vessels, in the interstitial tissues of the myocardium or beneath the endocardium, and rarely in the valves or endocardium. In experimental amyloidosis, deposits occur commonly in the myocardium.

Amyloidosis Associated with Multiple Myeloma. The findings in this disease are usually similar to those in secondary amyloidosis, and involvement of the heart is slight. Less commonly, the distribution of amyloid is the same as in the primary form.

Amyloid Localized in the Heart. King (1948) and Dahlin and Edwards (1949) have described cases in which localized deposits of amyloid were found in the heart and in no other organs. All of their patients were relatively old, ranging in age from 63 to 100 years. In most of the cases the amyloid could be recognized grossly, particularly beneath the endocardium of the atria. The deposits were minute, translucent and pinkish gray. Both atria were involved with equal frequency. The right atrium near the mouth of the coronary sinus and the intima of the coronary sinus for a distance of about 2 cm. were the most common sites, whereas in the left atrium the regions most commonly involved were the posterior wall and septum. Microscopically the amyloid was discovered to be in the loose connective tissue in the atrial endocardium. In the myocardium it showed the same pattern as in primary amyloidosis.

Staining Reactions of Amyloid. In sections stained with hematoxylin and eosin, amyloid has a homogeneous, amorphous character, staining pink, but usually not so brilliantly as collagen, and lacks the fibrillar nature of collagen. It exhibits metachromatic staining with certain basic dyes such as methyl violet and crystal violet, and stains light blue with anilin blue and methyl blue With congo red it stains deep red. Amyloid assumes a yellow color with the van Gieson stain; rarely there is a slight pink cast, but never the bold red of collagen; this is a helpful characteristic in distinguishing deposits of amyloid from colloid. King has described the ability of amyloid to combine with ammoniacal silver without the use of any reducing agent and has devised a histochemical method

based on this observation. Amyloid also is dimly fluorescent under ultraviolet light.

Gouty Heart. The heart may be affected in gout although actual tophi are rarely found. When they do occur it is usually in the endocardium and the mitral valve. In order to make the diagnosis, positive identification of the presence of appreciable amounts of uric acid in the tophi is important, because small amounts of uric acid may be deposited directly from the blood upon previously existing deposits of phosphate and carbonate of lime. Many of the cases reported in the literature fall into this latter category (Sodeman, 1941). However, Bunim and McEwen (1940) have reported an acceptable case of gouty tophi in the heart valves.

Hypertension and hypertrophy of the heart may result if there is accompanying renal disease. It is said that the incidence of hypertension and arteriosclerosis is higher in young gouty persons than in young persons suffering from other types of chronic disease. This increased incidence of hypertension and arteriosclerosis is less noteworthy in older age groups (Talbott, 1943).

Disturbances of Fat Metabolism

Fatty Change in the Heart. Two varieties of fatty change occur in the heart. (1) fat infiltration, which is an increase in subepicardial fat with infiltration and replacement of the myocardium by fat, and (2) fatty degeneration, which affects the sarcoplasm, and occasionally the nuclei, of the myocardial fibers This classification is useful because there are clinical, pathologic and etiologic differences between the two conditions. Fat infiltration "affects cells which normally contain fat and represents an alteration simply of the normal fat depots and transport" (Saphir and Corrigan, 1933), whereas fatty degeneration is a deterioration of the myocardium caused by the action of some injurious agent, often a toxin, whereby fat, lipoid or lipids accumulate in the myocardial cells.

Fat Infiltration of the Heart. Fat infiltration means, primarily, an excess in the deposit of normal fat. Fatty infiltration, therefore, is found in locations in which fat occurs normally. In the heart it is found in the subepicardium of the anterior wall of the right ventricle. Grossly the excess of fat is easily recognized on opening the right ventricle and atrium and exposing the tricuspid valve. However, in addition to the excess of fat, in fat infiltration there is also an extension of the subepicardial fat tissue into the myocardium with replacement of muscle fibers. Early fat infiltration is seen here exclusively, and advanced infiltration is most marked in this location. Normally there is a sharp demarcation of the subepicardial fat tissue from the myocardium. In fat infiltration the fat extends somewhat like the cells of a malignant tumor into the myocardium of the right ventricle and there is no clear-cut demarcation betwen the subepicardial fat and the myocardium. In this process, an excess of fat precedes the infiltration. This excess of fat causes pressure atrophy and leads to disappearance of the muscle fibers and their replacement by fat. The process may continue until the entire myocardial tissue of the right ventricle in a certain area is replaced by fat. This may be noted particularly at the apex and, in advanced cases, the fat may also be observed just beneath the endocardium.

Fat infiltration also may involve the left ventricle, where it is seen best in the form of plaques or circumscribed areas just beneath the endocardium, covering the interventricular septum. Often it follows the course of the left bundle of His and its ramification. Since no extension of the subepicardial fat tissue is demonstrable in these instances, it must be assumed that there is an excess of the minute amount of fat which may normally be present

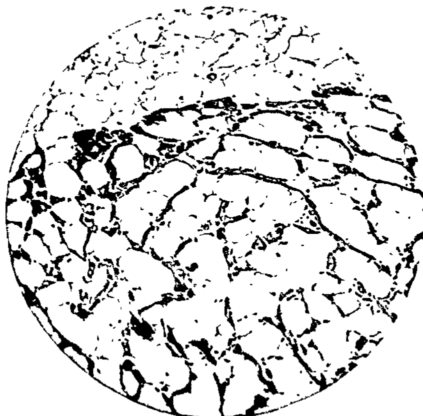


Figure VI-4 Subendocardial fatty infiltration of right ventricle X 175. (WCGH, 40 A 9)

adjacent to these subendocardial fibers. Monckeberg (1924) attributed unexpected death to infiltration of the bundle by fat.

Microscopically, the excess of fat cells and the atrophy of muscle bundles and individual fibers, in the absence of any cellular infiltration (Figure VI-4), are easily demonstrable It is also easy to discern the presence of fat tissue between muscle bundles and its extension into the myocardium at a distance from the subepicardial fat. The excess of fat is often noted first in the perivascular areas

Fat may also infiltrate the atria, more commonly the right atrium than the left. It is possible that some forms of cardiac arrhythmia or electrocardiographic changes may be induced by infiltration of fat with compression of the sinus node.

Clinically the signs and symptoms of fat infiltration should be those of right heart failure. Yet fat infiltration of the myocardium is practically never diagnosed during life. It stands to reason that a right ventricle partially replaced by fat would have diminished reserve power. While it may cause death rarely, it often serves to explain death of a patient who has relatively little bronchopneumonia or small pulmonary emboli. In these instances it is the right ventricle which is called upon to do extra work. A right ventricle with much of its myocardium replaced by fat may not be able to compensate for the slightly increased demand upon it and such a patient may die, sometimes unexpectedly, in the absence of premonitory symptoms.

The occurrence of rupture of a heart from severe fatty infiltration is questionable. A number of such instances are described in the older literature, and in 1939 an example was reported by Donat. If rupture occurs at all, it is extremely rare

Fat infiltration is often found in the



Figure VI-5 Fatty degeneration of myocardium of papillary bundles of left ventricle (WCGH, 49 A 50)

markedly obese and may also be present in the heavy beer drinker The so-called "beer-drinker's heart" of the old literature was a heart with fat infiltration However, fat or fatty infiltration of the heart also occurs in the absence of obesity Other terms used for this entity are fatty heart and lipomatosis of the heart (lipomatosis cordis)

Fatty Degeneration of the Myocardium. Fatty degeneration denotes excessive accumulation of fat and fatty substances in the myocardial fibers The fat occurs in the form of droplets most commonly in the cytoplasm but also in the nuclei Dible (1934) recognizes two forms of fatty degeneration One form is patchy in distribution, having the well known thrush-breast gross appearance (Figure VI-5), while the other is diffuse and causes the myocardium to look greasy. Although it is not known whether they are entirely distinct lesions or may progress from one to the other, nevertheless it seems desirable to retain the distinction until more is known of the nature of this disorder.

Fat content of normal myocardium. According to Dible (1934), the fat content of normal myocardium, after removal of the subepicardial fat and the fat adjacent to the coronary arteries, is 1.74 per cent with a range of 1.4 to 2.1 per cent, and the corresponding iodine value is 123 with a range of 118 to 130.

These values were obtained from the hearts of presumably normal persons who died either accidentally or from diseases which produced no detectable pathologic change in the heart. The fat content was determined by the method of Leathes and Raper and the iodine values by Dam's method. There was no difference between the fat content of the subepicardial half and that of the subendocardial half of the left ventricle Dible reported that the fat content of children's hearts is lower than that of adults, but gives no data in support of this statement He asserts that the fat content of the cardiac muscle reflects to some extent the general state of nutrition of the body, but that the range of variation in the amount of fat is not wide, if the extremes of inanition and obesity are excluded.

Patchy type of fatty degeneration of myocardium. In this form of fatty degeneration the changes are fairly sharply limited to the subendocardial portion of the myocardium, particularly the interventricular septum of the left ventricle, the papillary muscles and occasionally to corresponding locations in the right ventricle (Dible, 1934). Localization in the subendocardial portion of the myocardium and the papillary muscles of the left ventricle suggests that patchy fatty degeneration may occur more frequently in some muscle bundles than in others, for this is the distribution of the superficial sino-

spiral and bulbospiral muscles of the left ventricle. Such an explanation would also account for the infrequent involvement of the right ventricle, for these muscles do not make up the papillary muscles or subendocardial layer of that chamber (Lowe and Wartman, 1944).

The characteristic gross manifestation appears in the interventricular septum and consists of a peculiar yellow mottling which has been likened to the breast of a thrush or the coats of the tiger and tabby cat. The changes are most marked in the inner portion of the ventricular muscle beneath the endocardium, although minor amounts of fat can occasionally be detected in other parts of the heart.

Microscopically the patchy character of the lesion is also apparent, the areas of fatty degeneration being separated by myocardium which shows either minimal changes or none at all. The fat is found within the cytoplasm of the myocardial fibers in the form of globules which may be so large as to disrupt the fibers.

Dible found that while the fat content of the myocardium in apparently normal areas was 2.3 per cent, in visibly degenerated areas it was 3.5 per cent, an increase of 52 per cent over the fat content of normal heart muscle. The mean iodine values for these areas were 110 3 and 92 5, respectively.

Diffuse type of fatty degeneration of myocardium. In the diffuse type the myocardium is pale and greasy. It is also soft, friable and generally flabby. Both the right and left ventricles are involved about equally. Microscopically the fat globules are small and so diffusely distributed that every fiber is peppered with them. The entire thickness of the interventricular septum is affected and there is no difference between the fat content of the inner and outer portions.

Chemical analysis of the left ventricle showed that it contained an average of 3.3 per cent of fat which is an 80 per cent increase over the mean value for normal left ventricle. The iodine value was 104 (Dible, 1934). Kaufmann (1929) states that Krehl found 26 per cent of fat in the cardiac muscle of a person with phosphorus poisoning (ether extraction of dried myocardium), whereas by the same method normal myocardium contained 11 per cent of fat. Chemical methods indicate that the heart contains no protein-bound fat although histochemical methods suggest that some of the fat may be bound to protein.

There is no agreement among clinicians concerning the clinical manifestations of fatty degeneration of the myocardium. Cases have been described in which the patient's death was attributed to a severe degree of fatty degeneration (Garvin, 1940). On the other hand, in some advanced cases death cannot be attributed to it.

Fatty degeneration of myocardium in newborn. Rarely a newborn child, usually a robust infant, will develop cyanosis, hemoglobinuria, icterus and shock on the first day of life and autopsy will reveal severe fatty degeneration of the heart and liver, with multiple punctate hemorrhages in all organs. This condition has been given the name of *Winkel's disease* in the German literature and, if the cyanosis is particularly marked, it is called *Buhl's disease.* Both are usually associated with a progressive, septic infection. In Buhl's disease the umbilicus and intestines are usually infected, but in Winkel's disease they are spared and there is commonly an infection with *Bacillus (Escherichia) coli* (Kaufmann, 1929).

Fatty Degeneration of Endocardium. Fatty degeneration of the valvular endocardium occurs in the form of white and yellowish white plaques on the atrial aspect of the mitral and tricuspid valves, usually at or near the base, and is often

associated with calcification. Microscopically numerous cells are filled with fine fat droplets which lie between the connective tissue cells. Calcium may be present and, in some cases, small mononuclear cells are also found.

These lesions are common in old people, but may be seen in children or young adults who have died from anemia, intoxication or infection. They are thought to result from the mechanical effects produced by *closure of the valve during systole* (Kaufmann, 1929).

General Remarks. Fatty degeneration of the heart may result from quantitative or qualitative alterations of the blood especially in pernicious anemia or leukemia. It is common in acute infections, especially diphtheria, scarlet fever, sepsis or other infectious diseases accompanied by toxin production and high fever. It follows intoxication with phosphorus, arsenic, chloroform, iodoform, ether, alcohol and eating of poisonous mushrooms Partial or complete obstruction of the coronary arteries and long-standing pericardial exudate are said to cause it Kaufmann (1929) reports that fatty degeneration of the myocardium was present in 50 per cent of his cases of cardiac hypertrophy due to valvular defects, kidney disease, emphysema or kyphoscoliosis. He mentions that when valvular defects are present there is often marked fatty degeneration of the papillary muscles, particularly in the left ventricle

There has been considerable discussion in the past as to how the fat gets into the myocardial fibers. The work of Dible (1934) and of Dible and Gerrard (1938) indicates that the fat may be brought to the heart from the body depots and represents a true infiltration of the cell in the sense of Virchow's concept. Modern histochemical studies have also shown that when cells are injured they may imbibe water or other fluids from their external environment and become swollen. During this process lipids or lipoproteins may be precipitated and become visible as fine sudanophilic granules in the cytoplasm. This process is referred to as *fat phanerosis* in the older literature.

The Heart in Lipidoses. The heart may be involved in the lipid-storage diseases, focal accumulations of foamy cells being deposited in the endocardium or the arteries. Lesions may be found beneath the endocardium of the ventricles or atria and *in the myocardium, and consist of nodular* aggregations of foam cells and a reactive low-grade inflammation. The foam cells may contain lipids of different sorts, depending upon the disease process, or may contain no lipid. In the coronary arteries the patches may cause occlusion with resulting myocardial infarction and death. There are no special features of the lesions of the heart in this disease.

Disturbances of Carbohydrate Metabolism

Glycogen Disease of the Heart. Glycogen disease is basically a defect of glycogen metabolism. It is rare and it usually occurs in infants The heart may be the seat of predominant involvement, in which case it is usually spoken of as glycogen disease of the heart or *cardiomegalia glycogenica.* In another form of the disease the liver shows predominant involvement while the heart is usually slightly involved and not increased in size. In most cases of glycogen disease of the heart there is no gross involvement of the liver or other organs, but microscopically glycogen may be found in many organs of the body.

Gross and microscopic pathology. In those cases in which the heart is predominantly involved it is distorted and round in shape, so that both ventricles contribute to the formation of the apex. The heart may be enormously enlarged. The thickness of the myocardium of the left ventricle may measure as much as 29 mm. and of

the right ventricle, 9 mm. Cases have been reported in which the heart weighed as much as 260 grams in children less than four years of age. The muscle has a rather glassy homogeneous appearance but is not usually as gray as in amyloid disease. The columnae carneae are considerably flattened because of the hypertrophy and dilatation. The valves and coronary arteries are not involved.

Microscopically the appearance is quite characteristic The myocardial fibers are large, measuring as much as 50 micra in diameter, and there is extensive vacuolization of the sarcoplasm, the vacuoles giving a positive reaction with Best's carmine stain and with the iodine stain for glycogen Both stains are apparently reliable and give similar results The heart fibers may be changed almost beyond recognition and, when cut tangentially, may appear as hollow cylinders surrounded by a delicate, striated, protoplasmic wall The nuclei are compressed and displaced to the periphery. Often the most marked deposits of glycogen are just beneath the endocardium (Haymond and Giordano, 1946)

Several cases have been reported in which a slight degree of aortic stenosis was associated with the glycogen infiltration of the heart.

Age incidence Nearly all the cases which have been reported have occurred in children between the ages of four months and one year, and usually death has been sudden. In a few cases the children lived to the age of four years.

Chemical analysis of organs. Chemical analysis of the tissues from cases of glycogen disease of the heart are reported by van Creveld (1939). He gives the percentages of glycogen in the various organs as follows: heart, 7.97; liver, 9.13; spleen, 1.46; adrenal, 1.25; skeletal muscle, 9.39; lung, 0 03; spinal bone marrow, 0 583; while the amount present in the blood after death was 18 mg. per 100 ml. The percentages in a control case with marked hypertrophy of both ventricles due to a patent interventricular septum were as follows: heart, left ventricle, 0 055; heart, right ventricle, 0.07, liver, 0.103; kidneys, 0.062; spleen, 0.01; muscle, 0.011; the amount present in the blood during life was 12.75 mg. per 100 ml. The glycogen is usually deposited in the following locations: the fibers of the heart muscle, the liver cord cells, especially at the periphery of the lobules; the primitive bundles of the skeletal muscles; the convoluted tubules of the second order and collecting ducts of the kidney; the splenic pulp, especially at the borders of the follicles; the zona reticularis of the cortex of the adrenal; the spinal bone marrow; the cell bodies of ganglion cells; hair follicles of the skin; the walls of blood vessels; and the connective tissue cells in most organs.

A peculiarity of this disease is that the glycogen apparently does not break down, and hence is found in the organs for a long time after autopsy and even after the organs have been fixed in aqueous solutions This is in marked contrast to the behavior of glycogen in most other diseases and in normal organs from which it disappears promptly after death unless special measures are taken to preserve it. In glycogen disease the glycogen is usually well preserved for as long as several months and can be easily stained with routine glycogen stains after this length of time, even though the fixing fluid has been repeatedly changed. Finkelstein (1936) was able to demonstrate the presence of glycogen in the heart 13 years after it was placed in fixative. The glycogen may also be preserved by refrigerating fresh organs.

Pathogenesis. The pathogenesis of this disease is unknown at the present time. It is a disease of infants and occasionally shows a familial occurrence. It is believed that there is impairment of the normal

reversible process of conversion of glucose to glycogen The literature on the subject is reviewed and the various theories are discussed in the article of van Creveld (1939)

Circumscribed Glycogen Disease. Besides the diffuse form which has been described above the glycogen may be deposited focally. This form is sometimes called circumscribed glycogen disease of the heart or *cardiomegalia glycogenica circumscripta* (Finkelstein, 1936). In these cases there is usually, in addition to the glycogen infiltration, an increase of connective tissue with necrosis and fatty degeneration of the myocardial fibers. The glycogen is usually distributed subendocardially but not exclusively so

Congenital Nodular Glycogenic Infiltration of the Myocardium (Rhabdomyoma) is described on page 881

Disturbances of Calcium Metabolism

Calcification of the heart may be either dystrophic or metastatic, the former being much more common.

Dystrophic calcification may occur in any area of dead tissue that is not infected and that is so large or so situated that it cannot be absorbed. Hemorrhagic extravasates are particularly susceptible to calcification as are hyalinized scars Calcification of hyaline scars may occur whether necrosis is present or absent, it has been related to low production of carbon dioxide in a slowly metabolizing tissue, with consequent development of a local zone of relative alkalinity and reduced calcium solubility. Dystrophic calcification may also take place without change of the physiologic levels of any of the chemical constituents of the blood (Gore and Arons, 1949)

Metastatic calcification, in contrast, is associated with increased availability of calcium and is usually accompanied by deposits of calcium in other organs, particularly the lungs, stomach, kidneys, spleen and liver. It is found in association with destructive bone lesions, hyperparathyroidism, hypervitaminosis D, and renal insufficiency In metastatic calcification, the deposits have a characteristic distribution, being much more likely to accumulate in tissues which have a hyaline structure. For example, the hyaline structure of elastic tissue serves to explain the involvement of arterial and endocardial (right atrial) elastica in metastatic calcification. The selective localization of metastatic deposits of calcium is to be explained not only by the increased availability of calcium, but also by the structure and physiologic activity of the involved tissues. Dystrophic calcification, on the other hand, owes its occurrence purely to local pathologic changes and has no characteristic distribution (Mulligan, 1947; Wells, 1925; Gore and Arons, 1949).



Figure VI-6 Calcification of pericardium resulting from pericarditis of unknown etiology Patient was a 54-year-old woman, an inmate of the psychiatric hospital (WCGH, 35 A 285)

Dystrophic *calcification of the pericardium* (Figure VI-6) may occur in rheumatic fever and tuberculosis and cause constrictive pericarditis. Calcium is deposited less frequently in pericarditis caused by other bacteria, among which

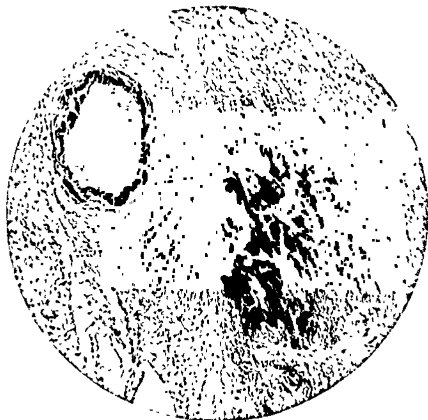


Figure VI-7 Calcification of pericardium resulting from excessive ingestion of Vitamin D Case of Dr W A Stryker. X 150. (WCGH, 45 P 101 E.)

may be mentioned pneumococci, streptococci and staphylococci. It may also be found in hemopericardium. Occasionally fibrous pericardial plaques ("soldier spots") may be calcified.

The valves of the heart are, of course, frequently the site of dystrophic calcification. Invariably there is previous valvular disease which is almost always rheumatic in origin (Karsner and Koletsky, 1947). Calcification of vegetations occurs frequently. Calcium may also be deposited at the base of the valves, particularly in the ring of the mitral valve, where it forms an annular structure usually on the ventricular aspect of the valve. These lesions are discussed elsewhere.

Calcification of the myocardium has been discussed at considerable length by Gore and Arons (1949). They found that the calcium deposits were laid down on necrotic muscle fibers. Ordinarily the necrotic material is absorbed before calcium is deposited. Thus, myocardial calcification is usually dystrophic. However, it may be metastatic, as for example in cases of *vitamin D intoxication* (Figure VI-7). Also, it is to be noted that under circumstances which favor metastatic calcification, there may be an augmented and accelerated tendency towards the development of dystrophic calcification. The process in the heart muscle in these cases is therefore regarded as an example of accelerated dystrophic mineralization. Renal failure and azotemia are usually present.

Gore and Arons believe that the laws of mass action and of ionic equilibrium of saturated solutions of poorly soluble salts explain, in the case of tricalcium phosphate, the ease with which precipitation may be induced by increases of either calcium or phosphate. According to these authors, the pathogenesis of the basic myo-

cardial lesion is varied, being due to ischemia, infection or unknown causes. They also point out the possible influence of uremia in causing multiple tiny foci of myocardial necrosis which subsequently calcify. Special staining reactions for iron and calcium showed the fallacy of making a diagnosis of calcification from a preparation stained with hematoxylin and eosin In three of their 13 cases the deposit proved to be iron only. In six others the calcium was associated, but not always coextensive, with iron.

When the calcification of the myocardium is massive, it may be detected in roentgenograms during life (Cutler and Sosman, 1924, Bishop and Roesler, 1934). Occasionally it is possible to diagnose cardiac aneurysm because the scar of the infarct is calcified (Parkinson *et al.*, 1938). Calcified nodules situated in the bundle of His may cause complete heart block (Yater and Cornell, 1935).

Calcification of coronary arteries is common and is discussed in Chapter VIII.

Pathologic Ossification. Heteroplastic deposits of bone have been described in the heart valves and in the myocardium of all chambers including the conduction system. Usually they are preceded by extensive calcification.

Finestone and Geschickter (1949) are of the opinion that if in addition to certain chemical criteria there is a diminished blood supply, calcium will be deposited in the tissues. If at a later date the blood supply is sufficiently improved by increased vascularity, such as may result from an inflammatory response to the presence of the calcium, then ossification may occur. In support of this theory they point out that the osteoblast is no longer regarded as a specific cell endowed with the power of producing bone, but that any connective tissue after preliminary dedifferentiation to primitive mesenchyme may be built up again in the form of any other connective tissue. Thus they believe that the only factors necessary for bone formation in mesenchymal tissue are an excess of calcium and an adequate blood supply. The presence of marrow cells has been explained in a similar fashion

THE HEART IN NUTRITIONAL DISEASES

Undernutrition and Starvation

Keys (1948) has summarized the cardiovascular effects of undernutrition and starvation. Both acute and prolonged undernutrition produce a reduction in the size of the heart comparable to the loss of weight of the body as a whole. Though reduction in epicardial fat is conspicuous, the major portion of the loss of weight is the result of reduction of the muscle in all chambers. Microscopically, there is first a reduction in the size of the muscle fibers. Later there is evidence of degeneration: cloudy swelling, loss of striation, vacuolization, and occasionally fatty degeneration The heart may also show brown atrophy.

The principal functional effect of undernutrition and starvation is reduction of cardiac output. Bradycardia may be pronounced, and there is reduction of systolic blood pressure, peripheral circulation, and venous pressure. While the presence of low venous pressure would seem to indicate that the cardiac state is not an important factor in the appearance of edema in starvation, it may be that physical exertion increases the venous return beyond the ca pacity of the atrophic heart. If this is th case, then famine edema may be esser tially the same as the edema of congestiv

heart failure from other causes, though the possible contribution of hypoproteinemia which accompanies undernutrition should not be overlooked It has been noted that starved persons may first develop cardiac failure following resumption of feeding.

The atrophy described above may be seen in the undernutrition of persons otherwise healthy who are deprived of adequate food or who restrict their intake, as in anorexia nervosa It occurs also in the course of chronic debilitating diseases such as cancer or tuberculosis, and such endocrine disturbances as Addison's disease and Simmonds' disease. Chronic constrictive pericarditis may cause atrophy of the heart and mitral stenosis, atrophy of the left ventricle only.

Nutritional Deficiency Diseases

The human heart is affected in thiamine (vitamin B_1) deficiency and potassium deficiency (Follis, 1948) and possibly in scurvy In animals, the evidence indicates that the heart may be affected when the diet is deficient in any of the following: vitamins B_1, C and E, potassium and copper

"Beriberi Heart." Thiamine or Vitamin B_1 Deficiency. More often than in any other vitamin deficiency, myocardial changes are found in Vitamin B (thiamine) deficiency. Mebius (1929) believed that a hydropic degeneration of the heart muscle fibers is the primary change in beriberi The right ventricle (pulmonary conus) is particularly involved. There is also some edema present, with only a few leukocytes in perivascular locations. Keefer (1930) noted dilatation of the right ventricle of the heart with fatty infiltration and moderate degeneration of the muscle fibers. Wenckebach (1934) also emphasized dilatation of the right ventricle, particularly in the region of the pulmonary conus. The right atrium was likewise greatly dilated, and there was interstitial edema of the myocardium. He also remarked on sarcolysis of the muscle fibers. This is described as giving the appearance of swelling and liquefaction to the entire muscle fiber. In spite of the swelling of the sarcoplasm, the striation may still be present. The interstitial edema is identical with that described by Eppinger and associates (1935) as "serous inflammation." The absence of any vestige of inflammation is also emphasized, in spite of the observation of Rossle (1934) who attributed sclerosis of the myocardium to serous myocarditis in a case of scurvy.

Grossly the heart is described as being globose with marked dilatation affecting predominantly the right ventricle, the wall of which may measure as much as 7 mm. in thickness. In adults, the heart frequently weighs 500 or 600 grams. The average weight reported by Dock (1940) was 629 grams. Edema, hydropic degeneration and slight scarring occur particularly in the subendocardial muscle fibers and the conduction bundle, and there may be marked edema of the interstitial connective tissues. Despite the edema and hydropic degeneration of the heart, the water content is said to be the same as that of normal hearts (Weiss and Wilkins, 1937). Fatty degeneration also has been reported and, according to Dock (1940), mural thrombi are constantly attached to the trabeculae carneae of the ventricles. The cases of occidental beriberi which Weiss (1940) studied showed simple dilatation in some instances and hypertrophy in others. The reason for the dilatation or hypertrophy is unknown, as there is no hypertension in beriberi.

Weiss and Wilkins (1937) remarked that of the vitamin deficiencies, lack of vitamin B_1 is the most important cause of cardiac disturbances. They stated that the myocardial disturbances reported in rickets and scurvy may be caused by a

simultaneous deficiency of vitamin B. The myocardium shows hydropic degeneration of the muscle fibers involving also those in the conduction system and there is an increase in the intercellular substance but an unaltered water content. Intercellular edema is to be noted. The same authors also found that in nine of 30 patients the heart showed an increase in weight and considerable dilatation of cardiac chambers, particularly of the right ventricle. Histologically, there were hydropic degeneration of myocardial fibers, swelling of collagen, perivascular edema and separation of myocardial bundles. It was also emphasized that the histologic changes were not regular, specific or even characteristic of beriberi. The microscopic lesions in the myocardium have been summarized by Follis (1942b). These lesions have been described in rats, dogs, foxes and swine Swank and Bessey (1942) observed myocardial changes also in pigeons. Most changes may be found in the hearts of swine There is vacuolization and hyalinization of the muscle fibers followed by necrosis. Later polymorphonuclear leukocytes and mononuclear cells are found. Both the atrial myocardium and the ventricular myocardium are involved, and eventually scar tissue is formed. Ashburn and Lowry (1944) remarked that both atria were involved in the majority of their animals with thiamine deficiency. Follis and associates (1942) observed that the heart muscle changes are quite similar to those observed in animals deficient in potassium. Blankenhorn and associates (1946) found degenerative changes in the muscle fibers, and interstitial edema in their 3 autopsied cases of occidental beriberi heart disease Alleman and Stollerman (1948) also reported myocarditis in an instance of beriberi heart disease. Microscopic sections showed extensive cloudy swelling, loss of striations, fragmentation and fatty degeneration of the muscle fibers, and necrosis There was also marked interstitial edema with small lymphocytic and leukocytic infiltrations. While the pathologist's impression was "subacute myocarditis of unknown origin," Alleman and Stollerman believe these changes to be consistent with the irreversible damage of chronic beriberi heart. It is interesting, however, that Follis (1942a) found that myocardial necrosis in rats on a low-potassium diet may be prevented by thiamine deficiency. In this connection Follis also stated that no anatomic lesions have been observed in the striated muscles of thiamine-deficient animals, however, foci of necrosis have been produced in rats in which there is a concurrent potassium and thiamine deficiency.

Rinehart and associates (1947) stated that major interest has revolved about the effect of thiamine deficiency on the heart, and that accumulated clinical and experimental evidence leaves little doubt that such deficiency results in a functional and structural defect. They found the right side of the heart to be dilated, at times appearing as if the muscle was stretched. Histologic examination revealed small foci of myocardial necrosis, as previously found in experimental thiamine deficiency in pigeons, rats and pigs. Another lesion was a well defined hydropic degeneration of myocardial fibers with hyperplastic nuclear changes, involving particularly subendocardial fibers, presumably of the conduction system. This lesion resembles that described by Wenckebach (1934) in human beriberi.

Microscopic necrosis has been reported in experimental thiamine deficiency in the following animals: swine, pigeons, dogs, rats (predominantly in the atria) and rhesus monkeys (Follis, 1948, Rinehart and Greenberg, 1949). The individual muscle fibers lose their striations and become hyaline and necrotic. Depending upon how long the animals survive, there

is lymphocytic infiltration and fibrosis, the scar tissue replacing destroyed muscle fibers. In most animal species these changes seem to affect the ventricles first, but terminally all chambers may be severely involved.

Scurvy or Vitamin C (Ascorbic Acid) Deficiency. It is known that children who have *severe scurvy may die suddenly.* Available but incomplete evidence indicates that this sudden death may be due to hypertrophy of the heart, especially of the right ventricle. The cause of the hypertrophy is unknown In 1918 Erdheim observed that hypertrophy of the right ventricle was present in about two-thirds of children dying of scurvy and that when the disease was severe both ventricles might be enlarged. No histologic studies were made in this respect Wolbach (1937) stated that degeneration of the cardiac muscle might occur. Follis (1942) described three infants who died suddenly of severe scurvy. At autopsy two of them showed hypertrophy of the right atrium, but careful histologic study revealed nothing of note

Experimentally various lesions have been attributed to deficiency of vitamin C. Fatty changes in the myocardium of pigs have been described by Bessey and associates (1934) Degenerative changes in the myocardium have been reported by Wolbach (1937), as well as along the line of closure of the cardiac valves in guinea pigs (McBroom *et al*, 1937) Nonspecific valvulitis, myocarditis and pericarditis have been observed in guinea pigs by Taylor (1937). Rinehard and Mettier (1934) studied the combined effect of scurvy and beta streptococcus infection in guinea pigs and observed lesions in the heart valves and myocardium *which resembled Aschoff nodules.*

Vitamin E Deficiency. Rats which have a vitamin E deficiency for long periods show extensive scarring of the myocardium (Mason and Emmel, 1945). The initial lesion is excessive deposition of ceroid in the myocardial fibers which is followed by necrosis. Connective tissue is increased and numerous macrophages filled with ceroid pigment are embedded in the collagen of this connective tissue.

Bragdon and Levine (1949) described actual foci of acute myocarditis in 15 of 17 *rabbits that developed severe muscular* dystrophy on vitamin E-deficient diets. In some instances, they also encountered foci of acute necrosis.

Deficiency of Potassium. It has been known for some time that diets *deficient in potassium* produce myocardial lesions. As Follis (1948) stated, when rats were kept several weeks on a low potassium regimen, tiny gray opacities are grossly observed in the ventricles. In animals that have been on a deficient diet for as little as eight days, microscopic studies reveal loss of striations in myocardial fibers which appear to be necrotic or hyalinized. Coincidentally with these changes the interstitial spaces are infiltrated by leukocytes. These lesions vary in extent; early in the course of the deficiency, the foci may be tiny, only one or two muscle fibers being involved, as the deficiency progresses, the areas are larger, being as much as two low-power microscopic fields in greatest diameter. In some hearts the tissues become diffusely infiltrated with leukocytes and are reminiscent of the lesions encountered in human myocarditis, such as that following diphtheria. Alterations are found in both ventricles, but are usually scanty in the atrial musculature. Blood vessels are normal, as are the epicardium and endocardium; no mural thrombi have been observed. In animals that survive longest there is usually an increased proliferation *of connective tissue at the sites of necrosis* of the myocardial fibers, so that scars of varying sizes are produced. Inflammatory lesions in the myocardium have been described also by Lowenhaupt and associ-

ates (1950). In early stages there is a clustering of polymorphonuclear leukocytes, and there are also eosinophilic cells and minimal necrosis.

Darrow and Miller (1942) produced cardiac lesions similar to those found in potassium-deficient animals by the injection of *desoxycorticosterone*. This adrenal hormone promotes excretion of potassium and retention of sodium Contrary to others, Follis (1948) remarked that nothing resembling an Aschoff body has ever been encountered in his own potassium-deficient material.

In adult cattle suffering from *copper deficiency* the heart may be the seat of extreme fibrosis, which is attributed to atrophy of the muscle fibers due to long-standing anoxemia (Bennetts *et al*, 1942) This is known as "falling disease" of cattle.

PIGMENTATIONS OF THE HEART

Endogenous Pigmentations

The heart may be pigmented in any disease in which there is diffuse pigmentation of the body

Hemosiderin. Deposits of hemosiderin, usually of microscopic size, may occur in areas of necrosis, such as infarcts and abscesses, or following trauma.

Hemochromatosis. The heart is involved in hemochromatosis in approximately 90 per cent of cases (Sheldon, 1935). The extent is variable and usually there are no gross alterations of the organ except for the brown discoloration. Sometimes the heart is small and the muscle soft. No gross changes have been recorded in the valves of the heart or the coronary arteries.

Hemosiderin is found constantly in the muscle fibers in nearly all cases The pigment is usually spread evenly through the organ The pigmentation may be so great that the muscle fiber appears as a sac completely filled with pigment Fine granules are first deposited at both poles of the nucleus, from these the pigment spreads longitudinally through the muscle fiber On cross section the granules are most numerous in the center of the fiber and least numerous at the periphery (See Figure VI-8) Degenerative changes, such as slight cloudy swelling and fatty degeneration, occur rarely. Occasionally there is an increase of fibrous connective tissue.

Hemofuscin also is found chiefly in the myocardial fibers where, like hemosiderin, it accumulates at the poles of the nucleus. This pigment is also found, both free and within phagocytes, in the vessel walls and the connective tissue of the interstitial tissues. It is not found in the endocardium, save for a small amount in an occasional phagocyte.

Bile Pigmentation. Bile pigment may be found in the myocardial fibers in patients suffering from jaundice. The pigmentation may lead to the development of cloudy swelling and fatty degeneration It produces diffuse pigmentation of the sarcoplasm and is best demonstrated in unstained frozen sections.

Lipochrome Pigment. Small amounts of lipochrome pigment may be deposited at the nuclear poles of the myocardial fibers in the form of yellow or yellowish brown granules. It is thought to be exogenous and to be introduced with foods (Connor, 1928). It may occur in association with brown atrophy of the heart.

Exogenous Pigmentation

The heart may be pigmented in silver poisoning, and occasionally deposits of anthracotic or silicotic pigment are found in the pericardium and interstitial tissues of the heart in cases of severe anthracosis and silicosis.

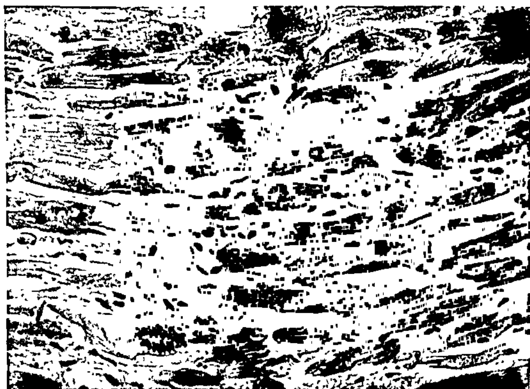


Figure VI-8 Hemochromatosis. Note deposits of hemosiderin and degeneration of myocardial fibers Patient was a 59-year-old man with hemochromatosis, who died of heart failure. X 400. (WCGH, 40 A 407.)

THE HEART IN ENDOCRINE DISEASES

Acromegaly

Cardiac failure is a common cause of death in patients with acromegaly, and at autopsy the heart is frequently large (Courville and Mason, 1938). The enlargement is most marked in the long axis. Histologically, there is hypertrophy of the muscle fibers and diffuse interstitial fibrosis, which may be so marked as to cause visible scarring (Cushing and Davidoff, 1927). The hypertrophy is usually explained on the basis of general splanchnomegaly.

Hyperthyroidism

There is a rather extensive literature on myocardial changes in hyperthyroidism, and many studies have been undertaken to determine if feeding with desiccated thyroid or thyroxin will produce changes in the heart muscle. Some of these references may be found in Saphir's (1942) review. Goodpasture (1921) reported the cardiac findings in 2 patients who evidently died of myocardial exhaustion. Microscopically, edema and focal necrosis were encountered. Willius and co-workers (1923) stated that histologically the myocardium of 18 patients showed swollen fibers with indistinct striations as well as marked fatty changes. Myocarditis was not mentioned. Lewis (1931), from a study of 12 necropsies of patients with hyperthyroidism, concluded that the changes in the heart were characterized by hypertrophy, dilatation and moderate fibrosis of the myocardium; that the cardiac damage may be fairly severe and that the cardiac disorder could not be relieved by treatment. There may also be toxic necrosis in the myocardium caused by toxic thyroid

secretion. He suggested that the increased work demanded from the heart results first in dilatation, then in hypertrophy, and renders the heart more susceptible to secondary noxious influences There was no interstitial connective tissue increase and no cellular infiltration. McEachern and Rake (1931) studied the findings in all cases of hyperthyroidism coming to autopsy at the Johns Hopkins Hospital since 1899. There were 27 cases. In 14 instances the hearts were grossly normal. In 8 instances they found moderate perivascular or intermuscular fibrosis or small foci of round cell infiltration. Cardiac hypertrophy was noted in 16 of 27 hearts. No relationship could be established between the incidence of atrial fibrillation or the duration of hyperthyroidism and the ultimate cardiac lesions

Rake and McEachern (1931) studied the pathologic changes in the heart and other tissues of animals with hypertrophy induced by thyroxin. The cardiac changes in the animals with hyperthyroidism were insignificant, and varied but little from changes seen in the normal control animals It was concluded that no significant alteration had been produced by hyperthyroidism Subsequently, Rake and McEachern (1932) stated that postmortem and experimental material indicated that hyperthyroidism itself produces no specific lesions in the myocardium They considered that the damage produced by physiologic wear and tear on the one hand, and by any associated infection or disease on the other hand, tended to be more accentuated in the patient with hyperthyroidism than in the normal person The evidence did not suggest the occurrence of a specific toxin producing specific myocardial lesions. It was felt that too much emphasis had been placed in the past on the morphologic changes in the myocardium with consequent neglect of important alterations in the metabolism and the function of the muscle fibers. These authors also suggested that perhaps the absence of glycogen in in the cardiac muscle in hyperthyroidism rendered the myocardium liable to injury, and that it reacts by diminished function. In this connection, it may be mentioned that McDonald and associates (1938) concluded that in hyperthyroidism, cardiac failure was not contingent on the presence or absence of glycogen. The function of cardiac glycogen was not primarily to produce energy, but, in some unknown manner, to act as a stabilizer between the conservation of energy and its expenditure. Likoff and Levine (1943) stated that it is apparent that thyrotoxicosis is not infrequently the sole cause of congestive heart failure. They did not, however, give a microscopic description of the cardiac findings.

In summary, as White (1944) has stated, there is no constant cardiovascular lesion in thyrotoxicosis In a few cases necrosis of the myocardium has been found, but this finding has not been confirmed as a thyroid effect. In severe thyrotoxicosis the weight of the heart is generally increased.

Hypothyroidism

Ohler and Abramson (1934) reviewed the literature on this subject. They quoted those who had expressed a belief in significant myocardial changes and contrasted this opinion with that of observers who held that the changes in the heart were of no great importance. Their own observations were based on a study of 35 patients with myxedema. One of these was examined postmortem, but unfortunately microscopic studies were not made The heart weighed 335 grams and there was edema of the epicardial fat tissue. The heart muscle grossly was translucent and light red.

Higgins (1936) commented on the confusion in the literature concerning cardiac lesions in myxedema. He pointed out that some authors had expressed the belief that

the changes were part of the hypothyroid state while others have indicated that they were incidental. He also mentioned that at the Massachusetts General Hospital in Boston only five autopsy records indicated changes in the heart in myxedema Four of these referred to interstitial edema with more or less fibrosis of the heart muscle fibers and one, to fibrosis only He believed that in the early stages of thyroid deficiency there is a mucoid infiltration of the muscle fibers which can be overcome by the use of thyroid extract. As the disease progresses, further degenerative changes occur, the heart becomes larger and coronary sclerosis develops. Because of these early and late changes, degeneration of the muscle fibers occurs and is followed by extensive fibrosis of the myocardium. He concluded that the condition of the heart in myxedema is a distinct clinical and pathologic entity and should be considered in the differential diagnosis of every obscure cardiac disease. Gordon (1935) expressed the view that the clinical features of "myxedema heart" were produced by pericardial effusion in the course of myxedema

Webster and Cooke (1936) studied morphologic changes in experimental myxedema in rabbits Microscopically, the heart muscle fibers from the myxedematous animals did not take the hematoxylin-eosin stain as well as those from the normal control animals. There was a striking increase in the size of the spaces between the individual fibers The fibers themselves were swollen, and the number of fibers per square millimeter was decreased. There was increased prominence of the longitudinal striations with partial disappearance of the transverse striations. The nuclei were pyknotic and surrounded by clear spaces. The increase in the perinuclear space was shown clearly in a cross section of the muscle bundle. Frozen sections stained with Sudan IV showed that there was little fat in the heart muscle and no fat in the clear spaces around the nuclei and between the fibers The authors stated that the heart muscle of these myxedematous animals had an average fluid content of 81.9 per cent, compared with 75.6 per cent in the control series. They concluded that myxedema was apparently capable of producing serious myocardial damage in the adult rabbit. It must be noted, however, that they terminated their experiments by killing the animals with carbon monoxide. Carbon monoxide (illuminating gas) also produces definite changes in the myocardium (see page 530).

Marzullo and Franco (1939) reported the occurrence of myxedema in a patient who died suddenly. The heart grossly and microscopically showed a normal myocardium. White (1944) stated that the occasional finding in myxedema of a well marked cardiac enlargement has led to the term "myxedema heart." He believes that the enlargement is the result partly of the dilatation and partly of the myxedematous change affecting the heart tissue (See also Schnitzer and Gutmann, 1946.) La Due (1943) presented the autopsy findings of a 52-year-old woman with myxedema who died of heart failure. The heart was enlarged and dilated, weighing 400 grams. Microscopically, the sarcoplasm of many heart muscle fibers was completely replaced by hydropic vacuoles An edematous material was also present between the heart muscle fibers but there were no cellular elements. These changes were more striking just beneath the endocardium.

Thus, in summary, it appears that there is no specific change within the myocardium which would warrant a diagnosis of either myocarditis or "myxedema heart." Changes similar to those occurring in the subcutaneous tissue or muscle tissues throughout the body may also be present in the myocardium.

ATROPHY OF THE HEART

Atrophy of the heart may be defined as a decrease in the size of the heart after it has acquired partial or full growth. In contrast to this is the congenitally small size of the heart, which is called cardiac hypoplasia. Atrophy is the result of ischemia and inadequate nutrition. Hence, it is common to find not only simple reduction in the size of the fibers, but also evidences of cellular injury such as cloudy swelling, fatty degeneration, pyknosis and even necrobiosis and lysis. The changes are thought to be brought about by enzymatic liquefaction of tissue proteins with formation of the same products which appear after hydrolytic cleavage of protein in the digestive tract, namely peptides and amino acids (Bradley, 1938).

The heart is reduced in size, frequently to two-thirds or one-half of normal. The apices of the papillary muscles are quite fibrous and the papillary muscles, especially of the left ventricle, are short and narrow so that the interpapillary spaces are pointed. The epicardium and the endocardium may be wrinkled and thick.

Microscopically the myocardial fibers first become smaller and then completely disappear, probably by autolysis (Karsner *et al.*, 1925). The reduction in the size of the heart is due to reduction in both size and number of the muscle fibers. They tend to become uniform in breadth, and large fibers disappear. The nuclei are also small and lie closer together than they do normally. The number of nuclei in the atrophic heart is greatly increased in proportion to the number of fibers and there is a relative increase in purine nitrogen. Frequently there is increased basophilia, but it is not known whether this is due to an actual increase in desoxyribonucleic acid or merely to condensation. No increase in mitoses occurs.



Figure VI-9 Serous atrophy of fat. Patient was a cachectic 46-year-old man who died of lymphoblastoma. (WCGH, 44 A 52.)

In *brown atrophy* there is striking accumulation of yellowish brown, granular pigment in the sarcoplasm, usually at the nuclear poles, about which it forms spindle-shaped figures. This pigment does not contain stainable iron. It is said to be largely hemofuscin associated with small amounts of hemosiderin (Connor, 1928). There is both relative and absolute increase in the amount of pigment. In severe cases the granules may be found not only within the muscle fibers but also scattered between them, probably as the result of destruction of myocardial fibers. The cement lines of the myocardial fibers are usually more distinct than normal.

Atrophy also occurs in a heart which was formerly hypertrophic. This is particularly common in emphysema or arteriosclerosis and in such cases the weight of the heart may be either within or above normal limits.

Atrophy of the heart may be seen in starvation, senility, as the result of endocrine disturbance, and especially as the result of wasting diseases such as tuberculosis and malignant tumors. The atrophic heart is usually considered to have a decreased reserve power

Serous (Gelatinous or Mucoid) Atrophy of Subepicardial Fat

Subepicardial fat may undergo a peculiar degenerative change which appears to be a combination of atrophy and edema. It is usually found in emaciated subjects suffering from senility or long-standing wasting diseases, such as tuberculosis or cancer. The fat is converted into a brown or reddish brown, translucent, wrinkled mass which looks gelatinous (Figure VI-9). Usually the coronary arteries are tortuous because they do not participate in the atrophy Microscopically the fat cells are distended with small droplets, which are often yellowish brown in color, and lie in the edematous ground substance of the pericardium. The individual cells undergo considerable alteration in size and shape so that many of them are round, spindle- or star-shaped. Indeed, the cells may become so small that they finally resemble fibrocytes.

EFFECTS OF DRUGS AND POISONS ON THE HEART

Only a general account of the effects of drugs and poisons on the heart is practicable here. The literature is vast. The morphologic changes produced by drugs and poisons are not specific. Similar lesions are produced by a wide range of toxic substances, differences are usually only those of degree and are dependent on the duration and intensity of the action of the substance. In general, these lesions consist of cloudy swelling or fatty degeneration of the myocardium, focal hemorrhages which are usually endocardial or epicardial but occasionally myocardial and, in more severe damage, focal myocardial necrosis Cellular exudates or infiltrates occur in some instances, usually in association with necrosis, and usually consist of lymphocytes and mononuclear cells. Occasionally the cellular component is a major feature of the microscopic picture. If the poisoned subject survives long enough, evidence of healing by fibrosis may be present. If the degree of damage is extensive, cardiac dilatation may be conspicuous, and if the toxic substance has resulted also in hindrance of the pulmonary circulation, the dilatation may be predominant in the right ventricle. The cardiac lesions in some instances are the result of a direct action of the toxic substance on the heart. More often, however, lesions either are secondary to alterations produced elsewhere in the body by the drug or poison, or represent a combination of direct and indirect effects Frequently it is difficult or impossible to distinguish direct from secondary effects in the heart of man or of an intact experimental animal, and conclusions in this respect may be only inferential. On the other hand, in experiments on the isolated heart, various cardiac effects induced by exposure to high concentrations of a substance may exceed or differ from those obtainable in the intact subject. In the latter the toxic substance may cause fatal disturbances originating elsewhere in the body before producing cardiac lesions comparable to those in the isolated heart.

Probably in most instances, the visible cardiac lesions resulting from poisoning or drug intoxication can be attributed in large part to insufficiency of oxygen supply to the cardiac tissue. The morphologic changes described above are similar to

those seen in anoxia or hypoxia from other causes, and the known effects of the toxic substance often include the induction of anoxemia Such substances as general anesthetics, hypnotics and sedatives of the barbiturate group, morphine and related narcotics, and a large number of industrial solvents may induce anoxemia by central respiratory depression Irritant gases such as phosgene, chlorine and sulfur dioxide cause anoxemia by inducing pulmonary edema or hemorrhage and hence interfering with normal respiratory exchange. Bronchopneumonia may occur as a terminal event in any kind of poisoning which is not immediately fatal and may affect the heart both by inducing anoxemia and

action.

[illegible] blood

[illegible] poison-

ing by arsine, or by inactivation of the oxygen-carrying capacity of *hemoglobin*, as in carbon monoxide poisoning. Exposure to bone marrow depressants such as benzol may cause anemia and thence anoxemia Respiratory enzymes in the cardiac tissue itself may be inactivated, as by cyanide compounds. A terminal oxygen lack may also be partly or largely responsible for cardiac lesions in instances of intoxication in which the liver, kidney, or intestinal tract are principally involved, though marked disturbances in the concentration or nature of other blood constituents reaching the heart may also be important when these organs are involved. Examples are the changes occurring in renal failure from mercuric chloride poisoning, hepatic failure in poisoning by carbon tetrachloride or chloroform, and *gastrointestinal involvement in arsenic* poisoning A variety of poisons and venoms may induce shock, and cardiac lesions which may occur consequent to this state.

If a toxic substance seriously affects more than *one organ*, then there may be multiple sources of cardiac damage. Chloroform, for example, may affect the heart not only indirectly as a result of hepatic damage or respiratory depression, but may cause direct cardiac damage as well, as evidenced clinically by the tendency of this compound to cause cardiac arryhthmia and ventricular fibrillation. Carbon tetrachloride affects both kidney and liver, again with secondary cardiac effects The hemolysis caused by arsine not only directly reduces oxygen supply to the heart but may lead to hemoglobinuric nephrosis, renal failure and consequent cardiac damage. *Phosphorus* poisoning may be a direct cause of pronounced fatty degeneration of the myocardium, and in addition causes widespread parenchymatous degeneration elsewhere. Poisoning by the mushroom *Amanita phalloides* causes dehydration from the gastrointestinal lesions, hepatic necrosis and renal degeneration, and in addition has a direct toxic action on the heart. Numerous other examples can be given.

In addition to the effects common to many of the substances so far discussed, certain of these compounds may have special or additional effects on the heart. In the course of inducing anesthesia, as by inhalation, hypertensive crises may occur, either as the result of asphyxia or of the release of epinephrine, with resultant acute cardiac dilatation, especially in the presence of pre-existing myocardial damage Purpura accompanying the thrombocytopenia of benzol poisoning may be manifest in the pericardial membranes and the endocardium. Hemorrhage may result from direct vascular damage by agents such as inorganic arsenic. In fatal salicylate poisoning, epicardial and subendocardial hemorrhages may occur as a result of hypoprothrombinemia, in methyl salicylate poisoning degenerative changes of the myocardium also may occur. In mercury poisoning, the disturbances in calcium-phosphorus balance as a result of renal

dysfunction may lead to deposition of calcium in myocardial fibers. Cadmium and phosphorus poisoning result in fatty degeneration of the myocardium, phosphorus particularly causing marked change of this type.

Carbon monoxide apparently causes damage solely by producing anoxemia, hence evidence of ischemia is more pronounced in fatal poisoning by this substance than in instances in which oxygen deficiency is only a minor or incidental effect. Beck and Suter (1938) point out the frequency of coronary thrombosis in patients who have suffered carbon monoxide poisoning and emphasize also that such poisoning may cause permanent cardiac damage, though it may not become apparent until long after seemingly complete recovery. Walcher (1939) reported 5 instances of carbon monoxide poisoning. The principal changes were hemorrhages in the pericardium and the myocardium, particularly in the papillary muscles. Microscopically, waxy degeneration, hemorrhages and infiltration by polymorphonuclear leukocytes were noted. He also mentioned frequent fragmentation of the muscle fibers, and suggested that the changes are in some respects similar to those seen in diphtheria. The degenerative changes, hemorrhages and necrosis occur primarily, while the inflammatory changes are simply secondary manifestations. Ehrich and associates (1944) in experimentally-produced carbon monoxide poisoning in dogs found, microscopically, hemorrhages and necrosis and what appeared to be degenerative changes of individual muscle fibers. Early calcification of necrotic fibers was also noted. From their experiments they concluded that in dogs severe changes in the myocardium are produced only if the concentration of carbon monoxide exceeded 75 per cent and was maintained at this level from 15 minutes to one hour, while moderate alterations were observed following chronic exposure, leading to a carbon monoxide hemoglobin concentration of 21 per cent. Multiple foci of myocardial necrosis were encountered by Neuberger and Clarke (1945) in a patient who was found unconscious and died 13 days later, without having regained consciousness. Most of these foci of necrosis were located just beneath the endocardium. Occasional petechial hemorrhages were seen also in otherwise intact areas of myocardium.

Drugs commonly employed for their therapeutic effect on the cardiovascular system, such as adrenalin, atropine, quinidine, digitalis, and thiocyanates, have not been shown conclusively to cause pathologic changes in man.

Myocardial changes in experimental animals are described after administration of *digitalis.* Histologic changes were produced by Dearing and associates (1943) in the myocardium of cats which were digitalized rapidly with a calculated therapeutic dose of digitalis, and were given daily quantities of the drug which were estimated to correspond to 3, 4, 5.5, or 6 cat units for a man weighing 70 Kg. The equivalent of three cat units daily of parenterally administered Digitoxin caused myocardial lesions within five days in one animal, whereas the same amount of orally administered tincture of digitalis produced myocardial lesions within 11 days in another animal. In the digitalized cats in this group, which received daily doses of digitalis in the toxic range, the myocardium was examined microscopically after a minimum of five days and a maximum of 30 days. Lesions were also produced by digitalis whole-leaf or by crystalline products of digitalis (Digitoxin, Lanatosid-A, Lanatosid-B and Lanatosid-C). The myocardial lesions were focal in distribution and were more frequent in the papillary muscles and in the left ventricular wall than in other regions. There was degeneration of muscle fibers and fre-

quently hemorrhage. Later, inflammatory cells were found, principally neutrophilic leukocytes, lymphocytes and histiocytes. Gradually, connective tissue cells (fibroblasts) proliferated. It may be of interest to mention in this connection that Kyser and associates (1946) showed that the cardiotoxic effects of digitalis in the dog may be modified by the use of aminophylline, theobromine sodium acetate, and atropine sulfate. Papaverine hydrochloride did not minimize the cardiac changes produced by administration of digitalis.

Experimentally in rabbits, injections of adrenalin have been followed by focal myocardial hemorrhages, degeneration, necrosis and lymphocytic infiltration, and later by replacement fibrosis and by hypertrophy.

Raab (1936) reported sudden death of a young athlete in whom at autopsy no lesion was found; chemical examination of organs for alcohol and poisons also was negative. An excessively high concentration of adrenalin-like substances was found in the heart muscle and was believed to be the immediate cause of death.

Alcohol produces the same lesions that are seen in respiratory depression of other kinds, when it is the cause of acute poisoning. In chronic alcoholism the changes are attributable not directly to the alcohol, but rather to the accompanying state of nutrition. Hence one may find severe fat infiltration in persons who have maintained a high caloric intake of food in addition to that of the alcoholic beverages consumed; on the other hand, if food intake has been inadequate, the changes described in nutritional deficiencies may be present.

Hypersensitivity to drugs may result in pronounced myocardial lesions. They have been noted particularly in hypersensitivity to certain organic arsenical compounds and to sulfonamides. Such reactions have a large inflammatory component and are dealt with in the Chapter on Myocarditis.

THE EFFECTS OF IONIZING RADIATION ON THE HEART

Warren (1942) has reviewed the effects of ionizing radiation on the heart. The severity of the changes depends largely on the amount of irradiation to which the subject is exposed. If we summarize numerous reports in which various amounts of irradiation were administered to experimental animals such as the dog, rat, rabbit, and sheep, the changes observed have included hyalinization of pericardial and epicardial connective tissue; edema, atrophy, and necrosis of myocardium, proliferation and hyalinization of interstitial tissue of the myocardium, focal lymphocytic and perivascular mononuclear and polymorphonuclear infiltration, perivascular edema, hemorrhage, and hyalinization, and vascular thickening. Prosser and associates (1947) report electrocardiographic abnormalities and evidence of cardiovascular failure in animals exposed to irradiation and in acute cases, at autopsy, cardiac hemorrhages of varied size and location.

In radiation therapy in man, according to Warren, little radiation reaches the heart unless treatment is directed at a thoracic or left mammary tumor, at the lower mediastinum, or at the esophagus. In 10 patients who received irradiation that included exposure to the heart, who lived two days to a year after treatment, Thibaudeau and Mattick (1929) observed changes ranging from slight interstitial fibrosis to hyaline and fatty degeneration and necrosis of the myocardium. Sometimes round cell infiltration was encountered. In other cases, granular and vacuolar degeneration of the myocardium and hyalinization have been stressed. Warren points out that, as else-

where in the body, "the various forms of cardiac damage secondary to radiation therapy cannot be recognized as specific in themselves, but the aseptic necrosis, hyaline fibrosis, and obliterative vascular changes combine to form a fairly characteristic lesion."

In swine exposed to total body irradiation from an atomic bomb explosion (Bikini) and dying one to 29 days later, the cardiac muscle rarely showed any evidence of injury, even hemorrhage being absent, (Tullis, 1949).

Liebow and associates (1949) have described the effects on man of the atomic bomb explosions at Hiroshima and Nagasaki. In patients dying within 14 days of the explosion, epicardial petechiae (Figure VI-10) were common and there was occasional edema about myocardial vessels. Similar changes were present in patients surviving to the seventh week, and in addition there were occasional endocardial and perivascular myocardial hemorrhages. In some instances there was subendothelial and myocardial exudation of plasma cells and small and large mononuclear cells. In 33 patients who died more than six weeks after the explosion, there were no significant cardiac changes except for focal hemorrhages and one instance each of "fatty change" and "focal necrosis."



Figure VI-10 Epicardial hemorrhages resulting from exposure to ionizing radiation (Courtesy, Armed Forces Institute of Pathology, Neg. HS 307 A.)

EFFECT OF DISEASES OF BLOOD ON HEART

Anemia

Severe, prolonged anemia may result in cardiac dilatation and hypertrophy and in fatty degeneration of the myocardium. Ellis and Faulkner (1939), among others, have observed cardiac enlargement roentgenographically in a majority of patients with chronic anemia of severe degree. With alleviation of the anemia, the size of the cardiac shadow may return to normal. While the roentgenogram does not permit distinction between dilatation and hypertrophy, analogy with the sequence of events in enlargement from other causes has led to the opinion that, in prolonged anemia, hypertrophy may eventually develop. Moreover, Cabot and Richardson (1919) found the weight of the heart increased in all but one of 19 patients dying with pernicious anemia, and in a study of cardiac enlargement in hookworm anemia, Porter (1937) reported a heart weight of 630 grams in one patient.

Fatty degeneration of the myocardium is a common postmortem observation in patients dying with severe anemia. The yellow subendocardial streaking and flabby musculature are typical findings. In young persons dying with severe anemia after gastrointestinal bleeding, Friedberg and Horn (1939) have observed also the presence of microscopic foci of myocardial necrosis.

In the past, cardiac lesions were commonly the result of chlorosis and pernicious anemia, but with the present rarity of chlorosis and the improved treatment of pernicious anemia, sickle cell anemia and secondary anemias have become the principal causes of such cardiac lesions

Present evidence indicates that the cardiac alterations in anemia are chiefly the result of impairment of oxygen supply. The degenerative changes are similar to those seen in anoxia from other causes and the cardiac enlargement may also be the result of myocardial injury. A less well-defined factor is the effect of the increased work which the heart performs in anemia This additional work is incurred in developing an augmented cardiac output per minute, to which both an increased rate and an increased output per stroke contribute Peripheral vasodilatation and diminished blood viscosity, which tend to diminish the work required of the heart, are also factors in severe anemia, and it is, therefore, difficult to estimate the importance of increased functional demands on the heart in producing morphologic alterations

It is well known that anemia can aggravate or precipitate myocardial failure in the presence of other cardiac disease and, conversely, correction of anemia may alleviate cardiac failure Similar effects have been noted in the clinical manifestations of coronary arterial disease Kinney and Mallory (1945) have reviewed the literature and in addition have reported the precipitation of cardiac failure and myocardial infarction in instances of acute anemia following hemorrhage from peptic ulcer. Anemia alone rarely causes congestive failure and seldom, if ever, is by itself a cause of fatal cardiac disease.

Polycythemia

In both primary and secondary polycythemia, there is an increase in the viscosity and the volume of the blood It has been thought that these changes impose a burden on the heart, leading to hypertension and cardiac failure White (1944) states, however, that peripheral vasodilatation largely prevents such an additional cardiac burden Norman and Allen (1937) found that the blood pressure in patients with polycythemia was no higher than in controls. Friedberg (1949) states that heart failure is a rare complication of polycythemia except where there is associated myocardial infarction or hypertensive and arteriosclerotic heart disease The latter conditions he considers to be coincidental That there is an increased tendency to thrombosis in polycythemia is well known, but Norman and Allen concluded that thrombosis of coronary arteries is less common than in the vessels of other organs. In their series of 98 cases of polycythemia vera, coronary disease was encountered in 5 patients, in one of whom a coronary arterial thrombus was found at autopsy.

Leukemia

Cardiac hypertrophy may occur in leukemia. The enlargement has been attributed in part to the associated anemia and in part to the increased metabolic rate. The subject is discussed in Chapter XII on Neoplasms

HYPERTROPHY OF THE HEART

Dilatation and Hypertrophy

Enlargement of the heart is one of the commonest of cardiac abnormalities. It may represent either dilatation or hypertrophy, or a combination of the two. At autopsy, the dilated heart is flabby, its chambers are enlarged and its musculature

is thinner than normal. The columnae carneae are flattened and the orifices of the valves may be enlarged because of dilatation of the ring Microscopically, myocardial fibers are thinned and elongated.

The term concentric hypertrophy (as distinguished from eccentric hypertrophy) indicates an increase in the mass of the ventricle with increase in thickness of its wall but a reduction in the lumen of the chamber. Karsner (1949) believes that this condition does not occur in life and that it is explained by postmortem rigor of the myocardium.

The hypertrophic heart is distinguished by an increase in the bulk of the myocardium, and hence in size and weight The heart may attain a weight of 1000 grams or more, but weights nearer 500 Gm. are much more common. A heart weighing 600 Gm or more is arbitrarily termed *cor bovinum* (Karsner, 1949). Simple determination of the weight of the heart is not a wholly reliable method of estimating the degree of hypertrophy. More accurate is the calculation of the ratio of heart weight to body weight (see tables, pages 968 to 973). The size of the heart as determined from its linear dimensions is a less accurate index of hypertrophy than is the cardiac weight, for these dimensions are affected also by the presence of dilatation.

Typically, the myocardium of the hypertrophic heart is firm and red, the pectinate muscles and columnae carneae are large and prominent, the papillary muscles are thickened, and often the mural endocardium is thick and opaque. Microscopically, the average thickness of the myocardial fibers is increased and their nuclei are large and rectangular. A slight degree of interstitial fibrosis is common.

Karsner and associates (1925) measured the thickness of myocardial fibers in a normal and in a hypertrophic heart. In each heart, the fibers varied considerably in size, but while the majority of fibers occupied an intermediate position within the range of fiber size in the normal heart, in the hypertrophic heart there were relatively few fibers in the lower or intermediate range and a large number in the upper range, *i.e.*, there appeared to be a tendency for the fibers of the hypertrophic heart to attain a uniform size. The authors concluded that the limit of hypertrophy of the heart is reached when all or nearly all the fibers have a uniform, maximum size.

In a similar study, however, Lowe and Bate (1948a) did not find such a tendency to uniformity in the fibers of hypertrophic hearts. In their material, the range of fiber size in the hypertrophic heart was wider than in the normal and the upper limit of fiber size was higher. Within this range, the majority of fibers fell in an intermediate position just as did the fibers in the normal heart The mean fiber thickness was about 13.4 micra in the normal heart and about 21.1 micra in the hypertrophic heart Interestingly, in two hypertrophic hearts, the fibers had similar ranges of thickness and similar mean size even though one weighed nearly 300 grams more than the other. The authors suggested that each heart had reached its limit of hypertrophy and attributed the difference in weight to a difference in the amount of interstitial tissue or fluid in the two hearts As factors determining the limit of hypertrophy, they considered the limitations on cellular nutrition in hypertrophy which have been pointed out by Harrison (1935) and Wearn (1941).

In general, the circumstances in which persistent cardiac enlargement is observed are of two sorts: those in which there is a structural or mechanical alteration in the channels of blood flow, and those in which there is damage to the myocardium. In certain conditions the two types occur together. It is even possible that the underlying cause of enlargement is the same in both types. The first group includes those

conditions in which abnormal communications exist between parts of the cardiovascular system; for example, congenital septal defects, persistent ductus arteriosus, arteriovenous aneurysm and incompetent cardiac valves. On the other hand, channels normally present may be absent or may be so altered as to resist the flow of blood, as in congenital valvular atresia, congenital or acquired valvular stenosis, coarctation of the aorta, and the vascular changes leading to systemic or pulmonary hypertension. The significant effect of these abnormalities, so far as cardiac enlargement is concerned, is either to distribute an excessive volume of blood to one or more chambers of the heart or to hinder the discharge of a normal volume of blood. In either event, the volume of blood to be discharged by the affected chambers becomes greater than normal and dilatation ensues

In the conditions noted above, dilatation or hypertrophy may occur in the absence of any discernible disease of the myocardium In the second group of lesions, there may be no mechanical cardiovascular defects, but because of damage to the myocardium, contraction of the heart is impaired, inflow tends to exceed output and the heart therefore enlarges. Any of the manifold causes of myocardial damage may have this effect Among them are ischemia or infarction resulting from coronary arterial disease, myocarditis of rheumatic or other origin, and degenerative changes resulting from diphtheria, anemia, nutritional deficiency, or toxic substances.

Of the conditions noted above, chronic valvular disease, chronic renal disease with hypertension, and coronary arteriosclerosis are the commonest causes of cardiac dilatation and hypertrophy. Less common are pulmonary hypertension, congenital heart disease, myocarditis and the degenerative lesions of nutritional deficiency, anemia and hyperthyroidism. Though hypertrophy has been induced in experimental animals by means of prolonged exercise, there is no convincing evidence in man of persistent cardiac enlargement as a result of athletics or hard labor

Occasionally in young adults, and infrequently in older persons, dilatation and hypertrophy of the heart with death in congestive failure occur in the absence of any of the recognized causes of cardiac enlargement. The myocardium may show only minute scars or there may be focal vacuolization of fibers or small foci of necrosis and of acute or chronic inflammation, but the lesions are inconstant and nonspecific, their significance is uncertain, and they are not associated with any constant factors in the clinical histories of the patients or in the manifestations of disease during life. (See Norris and Pote, 1946.)

In infants and children, cardiac enlargement generally occurs under the same conditions as in adults, though the relative frequency of the causative lesions is different. Congenital defects, for example, are much more common, and coronary arteriosclerosis is decidedly uncommon Moreover, a condition such as glycogen storage disease causes cardiac enlargement almost exclusively in infants and children inasmuch as subjects with this disease seldom survive to adult life. In a small number of cases among infants or children, no cause of cardiac enlargement may be discoverable. Such cases have been considered examples of "congenital idiopathic hypertrophy." In these cases the heart usually shows both dilatation and hypertrophy. The left ventricle is often principally affected and endocardial thickening is often conspicuous. Microscopically, changes in addition to hypertrophy are usually present. These include myocardial, endocardial and perivascular fibrosis, myocardial degeneration, occasional lymphocytic infiltration, or vascular changes such

as medial hypertrophy and intimal thickening Suggested causes include intrauterine or unobserved neonatal infections and hereditary factors which are perhaps associated with hypertension in the parent (Kugel and Stoloff, 1933). (See also discussion on Endocardial Sclerosis in Chapters V and IXB.)

Reference has already been made to the difficulty of distinguishing between dilatation and hypertrophy in living persons with cardiac enlargement. On postmortem examination of subjects in whom cardiac enlargement was of short duration, dilatation is usually found, while in patients with a prolonged history of enlargement, both dilatation and hypertrophy usually are present Moreover, at autopsy, cardiovascular lesions which morphologically are recent are likely to be accompanied by cardiac dilatation while those which are chronic are more likely to be accompanied by some degree of hypertrophy as well. Such observations have given rise to the opinion that dilatation of the heart regularly precedes the development of hypertrophy.

Experimentally, a similar sequence has been found. Eyster (1927) produced stenosis of the ascending aorta in dogs and observed that dilatation of the heart occurred either immediately or within a few days. In some instances the dilatation then subsided. During the succeeding three months, the hearts became hypertrophic.

Various explanations have been offered for the development of hypertrophy, of which the simplest has been that it is the result of increased cardiac work. A theory of nutritional deficiency attributes hypertrophy to inadequate blood supply. An increase in surface area relative to volume in the myocardial fibers as a result of stretching has been considered to be a mechanism whereby the nutrition and metabolic exchange of the fibers are improved and their size increased. A fourth possibility commonly offered is that hypertrophy is the result of injury to myocardial fibers, the injury constituting a pathologic nutritive stimulus.

The work of Eyster and his associates referred to above provides some evidence favoring the idea that injury is the stimulus to hypertrophy. Hydropic degeneration of muscle fibers was found in the hearts of dogs during the dilatation produced by stenosis of the aorta. If the stenosis was relieved during the period of dilatation, thus restoring the work load of the heart to normal, hypertrophy nevertheless developed at the same rate and in the same degree as in dogs in which the stenosis was maintained indefinitely. From these two observations it was concluded that injury to the heart is the stimulus to hypertrophy and that dilatation constitutes the injury. Observations in human heart disease are consistent with this view.

The relation of cardiac enlargement to cardiac function has also been the subject of much study. There is considerable evidence to indicate that dilatation and hypertrophy serve to maintain normal cardiac output, that is, that cardiac enlargement is a compensatory mechanism. As Friedberg (1949) has pointed out, cardiac enlargement appears when there is a disturbance of cardiac function, and it involves principally those chambers of the heart which are affected by the disturbance. Thus in aortic valvular disease, enlargement occurs principally in the left ventricle, and in pulmonary hypertension the right side of the heart is predominantly enlarged. Moreover, a heart which is enlarged may be able to maintain normal function, that is normal output, for long periods of time. Starling (1918) showed that, within limits, increased diastolic volume (dilatation) of the heart is accompanied by increased capacity of the heart to liberate energy for contraction. The increased power of contraction resulting from hypertrophy pro-

vides an additional means of preserving cardiac function in the presence of interfering lesions. It is to be emphasized, however, that cardiac enlargement has distinct limitations as a compensatory mechanism, and some of these are set in train by the enlargement itself. They are considered in the discussion of Cardiac Failure on page 540

Hyperplasia of the Myocardium

The occurrence of hyperplasia in adult cardiac muscle has been disputed for many years King (1940) and MacMahon (1937), among recent writers, claim that it does occur in certain circumstances. Other authors (Mönckeberg, 1924; Karsner *et al.*, 1925, Aschoff, 1936) state that enlargement of cardiac muscles occurs only by hypertrophy of the fibers. In order to establish direct proof of hyperplasia of the heart, one should be able to demonstrate (1) the presence of mitotic figures in the muscle nuclei, and (2) an increase in the total count of muscle fibers in the heart. Mitotic figures have been noted in enlarged hearts in infants and children (MacMahon) and in a young adult's heart which was undergoing repair (King). Recently, Lowe and Bate (1948b) have brought forth evidence for the occurrence of hyperplasia, by measurement of the diameters of cardiac muscles and their histologic appearance in an enormously enlarged heart of a young person with aortic stenosis They point out that the hyperplasia affected the muscle bundles of the heart independently, thus indicating that the individual muscles of the ventricle may react independently in disease.

Pulmonary Heart Disease (Cor Pulmonale)

Cardiac and circulatory disturbances resulting from diseases of the lungs or of the pulmonary blood vessels constitute pulmonary heart disease. The term pulmonary heart disease or *cor pulmonale* is not applied to the effects of pulmonary circulatory disturbances which are themselves secondary to lesions of the left side of the heart. Depending on its duration, cor pulmonale is manifested principally by dilatation alone or by both dilatation and hypertrophy of the right ventricle. If sufficiently marked, it gives rise to right-sided failure of the heart. The causes of cor pulmonale consist principally of those conditions which are known, or are reasonably assumed, to increase the resistance to the flow of blood through the pulmonary vessels and hence to cause pulmonary hypertension. Secondary factors in the production of heart disease of pulmonary origin include the effects of anoxia and of secondary polycythemia.

Acute pulmonary heart disease is frequently the result of pulmonary embolism, either a single massive embolus involving a main pulmonary artery, or multiple emboli involving several large branches may be responsible. If death does not occur immediately, right ventricular dilatation, and perhaps failure, may result. Rarely, however, a large pulmonary embolus or thrombus may be the cause of chronic cor pulmonale, death in right-sided failure occurring many months later. In such instances, as would be expected, right ventricular hypertrophy is present in addition to dilatation. In 8 of 42 cases of acute pulmonary heart disease following pulmonary embolism, Horn and associates (1939) report finding evidences of myocardial ischemia The lesions, including necrosis, resembled those of infarction following coronary occlusion. The changes occurred principally in hearts which were already the seat of other disease, particularly coronary arteriosclerosis. Suggested causes of the ischemia were reduced left ventricular output with consequent reduced coronary flow, anoxemia, and reflex coronary vasoconstriction. It was also suggested that increased ten-

sion in the right ventricle might hinder blood flow in vessels supplying that chamber.

In addition to pulmonary embolism, other acute conditions may be associated with the finding of right ventricular dilatation at autopsy, among them being pneumonia, exposure to irritant gases, and poisoning or asphyxia from various other causes In such circumstances, of course, cor pulmonale may be a minor or incidental factor in causing death

Chronic pulmonary heart disease usually has its origin in one of three types of disease (1) congenital defects involving an arteriovenous shunt, such as patent ductus arteriosus and cardiac septal defects, (2) chronic disease arising within the lungs, principally emphysema (including that in bronchial asthma), pulmonary tuberculosis, pneumoconiosis and pulmonary arteriolar sclerosis, and (3) kyphoscoliosis and other deformities of the chest In the congenital cardiovascular defects, the pulmonary circulation is subject to an increase in volume and pressure of blood, coming from the left side of the heart or the systemic circulation. In the pulmonary diseases, the circulation of blood through the lungs may be restricted by reduction in the vascular bed resulting from obliteration of blood vessels or by reduction in the size of vascular lumens or by alterations in the mechanics of respiration. Similar factors may operate in deformities of the chest and consequent emphysema, atelectasis, pulmonary hypoplasia, infection, and mechanical hindrance to breathing.

In a review of 18,000 autopsies, Griggs and associates (1939) found that right ventricular dilatation or hypertrophy occurred with the following frequency: 3.7 per cent in tuberculosis, 16 2 per cent in bronchiectasis, 28.9 per cent in emphysema, 54 2 per cent in pneumoconiosis, and in three of five patients with kyphoscoliosis. On the basis of postmortem observations, they made a diagnosis of congestive failure in 1.8 per cent of cases of tuberculosis, 4.4 per cent of bronchiectasis, 22 3 per cent of emphysema, and 50 per cent of pneumoconiosis.

Less common causes of impediment of the pulmonary circulation and hence of chronic cor pulmonale include the pressure of tumors and aneurysms in the mediastinum and the diffuse intrapulmonary vascular spread of metastatic tumor, particularly of primary carcinoma of the stomach.

Effect of Arterial Hypertension on Heart

Chronic arterial hypertension in the systemic circulation results in dilatation and hypertrophy of the left ventricle and frequently in similar but less pronounced changes in the right side of the heart In hypertensive patients dying of some noncardiac disease, only hypertrophy may be conspicuous, while evidence of dilatation is slight. If death in cardiac failure has occurred, however, then dilatation as well as hypertrophy is often striking. No other gross or microscopic changes in the heart are directly attributable to high blood pressure.

Endocardial thickening, especially in the left ventricle, and slight, often diffuse, myocardial fibrosis are commonly observed. These changes may be the result, however, of a deficiency of blood supply caused by coronary arteriosclerosis, which in some degree is a frequent accompaniment of hypertension. Friedberg (1949) cites the studies of Fahr and of others indicating the frequency of the association of hypertension and coronary arteriosclerosis in patients with clinical heart disease, and stresses the importance of coronary arteriosclerosis in accounting for clinical manifestations which are often attributed to high blood pressure alone.

THE EFFECT OF AGING ON THE HEART

It is difficult to separate the tissue changes produced by the process of aging from the pathologic monuments of diseases which may have been present earlier in life One cannot easily escape the conviction that in this field we are employing methods similar to those of the archeologist and that much of the evidence is necessarily circumstantial It is not justifiable to attribute the lesions found at autopsy in old people to age alone, unless the effects of previous disease can be excluded with certainty. This is a point which has been overlooked by many authors What is needed is not only a careful study of persons dying accidentally, but also a critical clinical and pathologic study extending over the entire life time of selected groups of individuals Obviously this would be a difficult undertaking.

Karsner's paper (1940) on the subject is the most critical and his remarks are worth quoting.

"In the last analysis, a machine wears out because of the destructive effects of friction Except for certain forms of arthropathy, it is difficult as yet to apply this conception to living organisms. The terms 'wear and tear' are too indefinite in meaning to be used appropriately in interpretation of aging of the human body. Often overlooked is the fact that man is subject to a wider variety and greater number of infectious diseases than any other creature, and, whilst much is known of these disorders, there are undoubtedly diverse effects in different parts of the body not yet adequately studied As progress is made, it is probable that many of the phenomena, vaguely referred to as due to 'wear and tear,' will prove to be residua of deteriorative processes initiated by infection

"The pathologist rarely sees an autopsy upon a person dead of old age In 400 autopsies upon persons over 65 years of age, Aschoff found no deaths attributable solely to old age (marasmus senilis, 'Altersschwäche'). . . . We have no record of it in more than 19,000 autopsies on people of all ages. . .

"What has been said in general terms applies also to the cardiovascular system. It is now known that, upon microscopic examination, the heart and aorta show a variety of inflammatory and degenerative lesions. . The changes often attributed to involution may be, in part at least, the sequels of disease long past.

"There have been various studies of the effects of aging upon the heart. Monckeberg quoted French authors to the effect that it is enlarged. Duthoit, Warembourg and Pinchart stated that this is true roentgenologically. W. Muller is said to have found that the highest average weight of the heart is in the seventh decade. It is probable, however, as Monckeberg suggested, that these studies have failed to take into account the effects of hypertension Aschoff, as the result of his observations, stated that the weight of the heart does not vary significantly from the normal. Kirch described a reduction in the size of the heart especially in its infrapapillary or apical portion. Aschoff agreed that this is true, but attributed it to reduction of coronary blood supply, rather than the effect simply of involution. Kirch distinguished between the gross appearance of senile atrophy and 'cachectic' atrophy, but the differences are not significant. Monckeberg, in particular, drew attention to the similarities of so-called senile atrophy and that which is a part of the general atrophy observed in nutritional edema. The conduction system does not share in the atrophy. It has been said that the heart weight: body ratio is reduced. In old age, however, the weight of the body is often

altered by atrophy of skeletal muscle, of fat and bone, so that the ratio is not altogether dependable. Kirch stated that the atria and the four valvular ostia are enlarged, and also that the mitral leaflets bulge toward the atrium in umbrella-like fashion, especially between the attachments of the chordae tendineae.

"This last change is occasionally found in persons of earlier life, when it is interpreted as due to disease and usually a disease that can be recognized; the same disease may have lost its identifying features in the aged This can also be said of increased depth of the sinuses of Valsalva and enlargement of the corpora arantii. Karsner and Koletsky and others have found that calcific sclerosis of the aortic valve is almost always due to inflammatory lesions especially those of rheumatic fever, rather than to aging Gross thought that coronary anastomosis increases with age, but Blumgart, Schlesinger and Davis related this change to disease rather than to age.

"Microscopic examination yields little, if any, further information What has been said above about atrophy is equally applicable here. It is said that the pigment in the fiber cells increases with age. Mönckeberg quoted Lubarsch as having seen outspoken brown atrophy in patients dead of inanition at from 25 to 39 years, and Prym as finding no real difference in this respect between the condition in old age as compared with inanition. There is no convincing evidence that this "Abnutzungspigment" is due to wear and tear or to disease. It is, however, a combination of lipid and pigment and is introduced in part at least in food, and the longer a man lives the more he may absorb.

"Miller and Perkins reported, on the basis of histological methods, that the heart of the aged shows an increase of elastica, but their method and the small number of observations do not provide convincing evidence. Aschoff quoted Rondolini as having found an increase of elastica in the nodes of the conduction system, but this also requires confirmation"

CARDIAC FAILURE

Heart failure has been defined as failure of the heart to maintain an adequate output of blood. The cardiac output may be inadequate to provide sufficient blood for the various and varying activities of the tissues of the body, and it may be inadequate to prevent the excessive accumulation of blood in the venous portion of the vascular system The precise relationship between these two features of heart failure is uncertain. It has been suggested that the primary effect of inadequate output is a deficient supply of blood to the tissues, that by some means at present unknown this deficiency of blood supply so affects the kidney as to lead to retention of sodium and water; and that, partly as a result of the consequent increase in blood volume and partly from further impairment of cardiac function, excessive accumulation of venous blood develops and the syndrome of congestive heart failure appears.

The commonest conditions in which congestive failure occurs are valvular defects, particularly of the mitral and aortic valves, chronic hypertension, and myocardial infarction following coronary thrombosis. Less common but important are severe rheumatic carditis, thyrotoxicosis, chronic pulmonary disease, congenital defects, anemia, and prolonged tachycardia. Infrequent or rare causes are arteriovenous aneurysm, cardiac trauma, thoracic deformities, external pericardial adhesions, tumors, and malnutrition (White 1944).

While congestive failure may occur during the course of any one of the conditions listed above, frequently the onset of failure is precipitated by the appearance of a process which either causes additional direct cardiac damage or requires an increased cardiac output. The complicating factor may be primarily cardiovascular or it may arise elsewhere in the body. The commonest precipitating cause of congestive failure is infection The heart may be directly involved, as in rheumatic carditis or subacute bacterial endocarditis. If the infection arises elsewhere, it may induce tachycardia, it may produce damaging toxins, it may cause coughing and attendant muscular exertion, and it may impair renal function, including the excretion of sodium Other precipitating factors are reduced coronary flow from any cause, changes in cardiac rate and rhythm, pregnancy and childbirth, hemorrhage, anemia, transfusions and infusions, pulmonary embolism, and physical and emotional strains

At autopsy of patients dying in congestive failure from any cause, enlargement of the heart is an almost constant finding Whether dilatation or hypertrophy is predominant depends upon factors which have been discussed in a preceding section (page 533) Evidence has been presented indicating that cardiac enlargement may be a compensatory mechanism by which the heart maintains its output in the presence of interfering factors Whether compensatory or not, cardiac enlargement is so common a forerunner of congestive failure that in most instances study of the heart in chronic congestive failure implies study of the enlarged heart

Chemical investigations have so far been unsuccessful in accounting for the onset of cardiac failure. Alterations have been observed in the concentration of potassium, and in the metabolism of glycogen and of such phosphorus-containing compounds as phosphocreatine and adenosine triphosphate, but an understanding of the significance of such changes is incomplete.

Morphologically, there are no specific gross or microscopic changes in the heart which has failed. The same types of lesions are seen in hearts which have failed and those which have not. Though in general the underlying disease is more advanced in hearts which have failed than in those which have not, exceptions are so numerous that postmortem examination of the heart does not yield reliable evidence as to whether failure was present in life.

Present explanations of heart failure of chronic congestive type chiefly involve consideration of the effects of cardiac enlargement. Reference has already been made to the presence of inherent disadvantages in enlargement of the heart, even though within limits enlargement may have a certain compensatory value It has been observed that dilatation permits the heart to develop greater energy of contraction only within certain limits Dilatation beyond the optimal point results in a falling off of cardiac output, partly as a result of the mechanical disadvantage to the myocardial fibers. In hypertrophy, as the myocardial fibers enlarge, their metabolic requirements increase, and at the same time it becomes more difficult to satisfy these requirements. The difficulty has several sources. More time is required for diffusion of oxygen, and probably of other substances, through a large fiber than through one of normal size. The greater part of the oxygen supply of the myocardium is brought to the myocardial vessels during diastole, when the coronary blood flow through the heart is greatest, but diastole is not increased in length in the hypertrophic heart. Moreover, there may be an actual deficiency of blood supply to the hypertrophic heart. According to the histologic studies of Shipley and associates (1937), Wearn (1941), and Roberts and Wearn (1941), there is no increase in the

number of capillaries supplying the myocardium in hypertrophy. Any augmentation of blood supply must therefore occur within existing channels. Harrison (1939) has calculated that in the hypertrophic heart the required blood flow may be two or three times greater than normal. In the absence of such increased flow the myocardium may be in a hypoxic state. With progression of the lesions initially giving rise to the enlargement, or with the supervention of additional damage to or demands on the myocardium, the inherent disadvantages of enlargement come to exceed any compensatory value it may have, the contractile power of the heart is no longer sufficient to maintain an adequate output, and congestive heart failure ensues.

Brief mention may be made of acute heart failure, in which the onset of failure is abrupt and the duration short. The effects of such failure are principally those of inadequate blood supply to such vital structures as the brain and the heart itself. If the patient survives, he may develop the syndrome of congestive failure. At autopsy, dilatation of the right side of the heart is often seen but, as in the chronic congestive form, there are no specific morphologic changes. One common cause of acute failure is sudden alteration in rhythm, which may be either of reflex origin or secondary to some other cardiac lesion, and which may consist of marked tachycardia of ventricular or atrial origin, bradycardia, or ventricular standstill. Other causes include acute cardiac injury, as in myocardial infarction, diphtheritic "myocarditis," or rupture of a valve, and sudden mechanical hindrance to the heart, as in cardiac tamponade, massive pulmonary embolism and obstruction of a valve orifice by a thrombus.

EFFUSIONS AND AIR IN PERICARDIAL SAC

Hydropericardium. The pericardial sac normally may contain as much as 50 ml. of clear, watery, pale yellow fluid having a low protein content and a low specific gravity. Pericardial fluid in excess of 100 ml. constitutes hydroepicardium Such fluid is to be distinguished from the serous exudate of pericarditis As part of a general tendency to accumulate fluid in the tissues or serous cavities, hydropericardium occurs most commonly in congestive heart failure, but it is also seen in subacute glomerulonephritis, nephrosis, myxedema and beriberi. Perhaps in part as a manifestation of nutritional hypoproteinemia, excessive pericardial fluid may accumulate late in the course of wasting diseases. Local impairment of venous flow may result in hydropericardium, as for example when veins draining the pericardium are compressed or obstructed by mediastinal tumors or inflammations.

The effects of hydropericardium depend upon the speed with which it develops and on the amount of fluid, the rate of accumulation being often the more important factor The normal pericardial sac is capable of expanding to hold a liter or more of fluid without exerting a serious compressive effect on the heart or on the veins entering the heart, provided that the accumulation is slow. But if the accumulation is rapid, even a few hundred milliliters may exert severe or fatal compression (cardiac tamponade) by restriction of filling of the cardiac chambers, particularly the atria, and by diminishing the flow of blood through the intrapericardial portions of the venae cavae and the pulmonary veins. If the parietal pericardium is thick-

ened by disease, compressive effects will be produced by slower or smaller accumulations than when the pericardium retains its normal expansibility.

Hemopericardium. The escape of unmixed blood into the pericardial sac has effects similar to those of hydropericardium but, *since hemorrhage is likely to be* more abrupt and is frequently abundant, cardiac tamponade is more likely to occur. Causes of hemopericardium include direct *trauma, rupture of pericardial vessels, rup*ture of the heart, and rupture of the intrapericardial portions of the great vessels Minor hemorrhage may occur as part of an inflammatory exudate or in metastatic tumor of the pericardium.

Pneumopericardium. Air may enter the pericardial sac and occasionally may cause cardiac compression. Traumatic perforation of the parietal pericardium is the usual means of entry. In the event of such perforation, the presence of air is likely to be obscured by other effects of the trauma. Air may also be introduced into the pericardial sac, either by accident or by intention, in the course of therapeutic procedures. Perforation of a neighboring air-containing organ into the pericardial sac has also been reported (Harp and Peeke, 1949).

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CHAPTER VII

Vascular Lesions of the Heart

A. Coronary Sclerosis

S. E. Gould

MORE PEOPLE die of disease of the coronary arteries than of any other disease. As man's life-span lengthens, the relative incidence of disability and of death from this cause continues to increase. It is encouraging, therefore, to note that increasing study is being devoted to the causes, treatment and prevention of coronary disease.

Galen (138-201 A.D.) first applied the name "coronary" to the larger arteries of the heart and Lobstein (1833) coined the term "arteriosclerosis."

The first correct diagnosis of coronary thrombosis made during life and verified at autopsy was reported by Hammer in 1878. His patient collapsed after an illness of 24 hours. Autopsy disclosed closure of the ostium of the right coronary artery by thrombotic masses which had their origin from the right aortic cusp (embolic bacterial vegetations). Dock (1896), Obrastzow and Straschesko (1910) and Hochhaus (1911) also reported instances of coronary thrombosis recognized during life, but the classic description of clinical coronary thrombosis with substantiation by autopsy findings was published by Herrick in 1912 (see historical account, page 11).

BLOOD VESSELS OF THE HEART

Anatomy of the Coronary Arteries. The coronary arteries are arteries of the fourth order, their caliber corresponding to that of the distal portion of the radial arteries. For the gross anatomy of the coronary arteries, see Chapter II, page 103. The coronary arteries are of muscular type (Wolkoff, 1929, Benninghoff, 1930), showing a sudden transition from the aorta, which is an elastic artery. The intima contains a subendothelial layer of connective tissue, next to which is a prominent elastic-hyperplastic layer and after this, in turn, a musculoelastic layer. The media is composed of circularly-disposed muscular fibers which are accompanied by elastic fibers. The elastic fibers are delicate in the inner half of the media and coarse in the outer half. No distinct *elastica externa* is present. The adventitia is composed of collagenous and elastic fibers and is not well developed. The coronary arteries are richly supplied with vasa vasorum. The coronaries, thus, are characterized by the thickness of the intima, a well-developed muscular media and a thin adventitial layer. The increase in intimal thickening affects particularly the first portion of the coronary arteries, the first portion of the main branches of the left coronary, and the main branches at the sites of origin of secondary branches. The changes of atherosclerosis, first with deposit of lipoid material, later with formation of collagen and finally with calcification, take place primarily in the elastic-hyperplastic layer. A c[illegible] of the main stems of the two co[illegible]

teries shows that in the left artery the intimal connective tissue layer is less well developed and the elastic-hyperplastic and elastic muscular layers are better developed, while the media contains relatively more and coarser elastic fibers (Benninghoff). It is believed that in the development of atherosclerosis, the initial deposit of lipoid material takes place primarily in the elastic-hyperplastic layer. This change is succeeded by connective tissue proliferation, formation of collagen or hyaline connective tissue and calcification.

Sex Difference in Coronary Arteries of Newborn. Dock (1946) studied sections of the main coronary arteries of 12 newborn infants of each sex He found that, on the average, the thickness of the intima in males was 26 per cent of that of the entire vessel, while in females it was but 8 per cent In other words, the intima of the coronaries in newborn males, on the average, was three times as thick as that of the coronary arteries of newborn females. He concluded that this difference in structure serves to explain the sex difference in incidence of coronary occlusion in later years of life. Fangman and Hellwig (1947) confirmed the findings of Dock, they believed that the intimal changes were not inherited but rather pathologic and represented the earliest stages of arteriosclerosis.

Changes in Coronary Arteries Attributable to Age. The principal change in the coronary arteries attributable to age is a thickening of the intima (Wolkoff, 1929). The thickness of the intima of the coronary arteries exceeds that of other muscular arteries and increases progressively with age. The considerable thickness of the intima of these vessels is related to the special mechanical factors, such as pressure and tension, to which these arteries are subjected. At birth the intimal layer is relatively thin and consists of a single well formed layer of elastic fibers (*lamella elastica interna*) which is covered by a layer of flat endothelium. In childhood, the thickness of the intima is about equal to that of the media, during the third and fourth decades intimal thickness becomes maximal; in middle age and in old age the intima is several times as thick as the media. This thickening chiefly involves the first portions of the main vessels and the sites of these vessels from which branches arise. It may begin to appear at birth or within a few months after birth. The thickening is brought about (1) by splitting off of the internal elastic lamina from the internal limiting lamella, with the formation of a *musculoelastic* layer; (2) by splitting of the internal limiting lamella with formation of a prominent *elastic-hyperplastic* layer; and (3) by formation, in most cases, on the inner aspect of the hyperplastic layer, of a layer of connective tissue. Bork (1926) observed splitting of the elastic layer of the intima in the youngest patient he examined, age one month; he recognized the musculoelastic layer as early as the sixth month of life and found the connective tissue layer to be well developed at age 15. Wolkoff (1929) found that after the fifteenth year the subendothelial connective tissue becomes thicker, and within it there develops a longitudinal layer of smooth muscle. These changes in the intima are fully developed at 30 years of age and occur earlier and more prominently in the left coronary than in the right. With increasing age, the intima develops nodular thickenings, the media becomes narrower, the adventitia thicker.

L. Gross and associates (1934) demonstrated changes in the myocardial arteries which are related to age and to location within the heart. These changes, which they call fibroelastic metamorphosis, consist of elastification of the media, elastic-hyperplastic changes in the intima, fusion of these two layers, atrophy of smooth muscle fibers and development of irregular patches of connective tissue. With re-



Figure VII-1 Heart and aorta of man of 94 showing dilatation of aorta with but minimal atherosclerosis (WCGH 49 A 453)

spect to time and frequency of appearance, these changes occurred earliest and oftenest at the following sites, in decreasing order: posterior papillary muscle of the left ventricle, interventricular septum, left ventricle, pulmonary conus, and atria.

The most important change caused by aging of the arterial wall in the larger arteries is a gradual diffuse distention (Ophuls, 1933a). This results from progressive deterioration of the elastic tissue and is not accompanied by any characteristic histologic change. Thus, in the prime of life, the circumference of the aorta at its root generally measures about 50 mm, but this increases to 70 or 80 mm or more with advancing age (Aschoff, 1933a). The stretching of the wall occurs in a transverse as well as in a longitudinal direction and, as a result, the aorta becomes wider and longer and assumes a tortuous course (Figure VII-1). The tortuosity of the coronaries may be accentuated by atrophy of the myocardium in old age and in wasting diseases.

Aside from this dilatation, the walls of the arteries increase in thickness, so that throughout life there is a constant increase in the total diameter of the coronaries as well as in the diameter of their lumina (Ehrich *et al*, 1931). Microscopically, the media shows a constant increase in number and thickness of elastic fibers, and in number of nuclei. These changes are progressive during succeeding decades, but are greatest in the first two decades during the period of greatest growth of the arteries and of the heart. During this same period of growth, the intima shows its greatest growth in the musculoelastic layer, therefore, the hyperplastic layer develops progressively until the end of life, probably in response to mechanical factors During the average span of life the cross-sectional area of arteries increases six to seven times and the number of macroscopically visible arteries is doubled, the small branches increasing by approximately 80 per cent. The number of vessels distributed to the pericardial fat also increases with age.

Blood Supply to the Heart. The distribution of the coronary arteries is described in Chapter III (see page 103). According to Ehrich, de la Chapelle and Cohn (1931), the right coronary artery supplies the upper two-thirds of the ventral, the lateral and dorsal walls of the right ventricle and the cephalic half of the mesial aspect of the dorsal surface of the left ventricle; the left coronary artery supplies the greater portion of the left ventricle (except for the cephalic half of the mesial aspect of the dorsal surface), the lower third of the ventral surface of the right ventricle and that portion which borders on the sulcus longitudinalis.

The ventral two-thirds of the interventricular septum and generally its apex are supplied by branches of the anterior descending ramus of the left coronary, while its dorsal third, except for the apex, is n

teries shows that in the left artery the intimal connective tissue layer is less well developed and the elastic-hyperplastic and elastic muscular layers are better developed, while the media contains relatively more and coarser elastic fibers (Benninghoff). It is believed that in the development of atherosclerosis, the initial deposit of lipoid material takes place primarily in the elastic-hyperplastic layer This change is succeeded by connective tissue proliferation, formation of collagen or hyaline connective tissue and calcification

Sex Difference in Coronary Arteries of Newborn. Dock (1946) studied sections of the main coronary arteries of 12 newborn infants of each sex. He found that, on the average, the thickness of the intima in males was 26 per cent of that of the entire vessel, while in females it was but 8 per cent. In other words, the intima of the coronaries in newborn males, on the average, was three times as thick as that of the coronary arteries of newborn females. He concluded that this difference in structure serves to explain the sex difference in incidence of coronary occlusion in later years of life. Fangman and Hellwig (1947) confirmed the findings of Dock, they believed that the intimal changes were not inherited but rather pathologic and represented the earliest stages of arteriosclerosis

Changes in Coronary Arteries Attributable to Age. The principal change in the coronary arteries attributable to age is a thickening of the intima (Wolkoff, 1929). The thickness of the intima of the coronary arteries exceeds that of other muscular arteries and increases progressively with age. The considerable thickness of the intima of these vessels is related to the special mechanical factors, such as pressure and tension, to which these arteries are subjected. At birth the intimal layer is relatively thin and consists of a single well formed layer of elastic fibers (*lamella elastica interna*) which is covered by a layer of flat endothelium. In childhood, the thickness of the intima is about equal to that of the media, during the third and fourth decades intimal thickness becomes maximal; in middle age and in old age the intima is several times as thick as the media. This thickening chiefly involves the first portions of the main vessels and the sites of these vessels from which branches arise It may begin to appear at birth or within a few months after birth. The thickening is brought about (1) by splitting off of the internal elastic lamina from the internal limiting lamella, with the formation of a *musculoelastic* layer, (2) by splitting of the internal limiting lamella with formation of a prominent *elastic-hyperplastic* layer, and (3) by formation, in most cases, on the inner aspect of the hyperplastic layer, of a layer of connective tissue. Bork (1926) observed splitting of the elastic layer of the intima in the youngest patient he examined, age one month, he recognized the musculoelastic layer as early as the sixth month of life and found the connective tissue layer to be well developed at age 15. Wolkoff (1929) found that after the fifteenth year the subendothelial connective tissue becomes thicker, and within it there develops a longitudinal layer of smooth muscle. These changes in the intima are fully developed at 30 years of age and occur earlier and more prominently in the left coronary than in the right. With increasing age, the intima develops nodular thickenings, the media becomes narrower, the adventitia thicker.

L. Gross and associates (1934) demonstrated changes in the myocardial arteries which are related to age and to location within the heart. These changes, which they call fibroelastic metamorphosis, consist of elastification of the media, elastic-hyperplastic changes in the intima, fusion of these two layers, atrophy of smooth muscle fibers and development of irregular patches of connective tissue. With re-



Figure VII-3 Roentgenogram of injected heart showing distribution of deeper divisions of coronary arteries (From Gross, 1921 [Figure 5, p 17] Courtesy of Paul B Hoeber)

In skeletal muscle, in renal glomeruli and in the skin, there is an intermittence of blood flow in the capillaries. The work of Wearn (1941) indicates that the heart, however, utilizes all of its capillaries at all times and that intermittence of flow through the coronary capillaries does not occur The percentage of oxygen saturation of coronary venous blood in the normal *heart (of the dog) at rest is considerably* lower than that of venous blood of skeletal muscle, in other words, the normal heart makes almost complete use of its available oxygen, and any increase in work of the heart must be met by an increase in the coronary flow.

According to Wearn, the number of capillaries per square millimeter in the human heart is approximately 4000 at birth and ranges from 3000 to 4000 (mean 3342 ± 36) *in* adults. At birth there is one capillary for each five myocardial fibers; *in the adult heart the ratio of capillaries* to muscle fibers is approximately 1:1. This capillary concentration remains fairly constant throughout adult life, as does the diameter of the muscle fibers in normal adult hearts (mean *diameter,* 14 *micra).* In hypertrophy of the heart there is no increase in the number of muscle fibers or capillaries, but the increased size of the fibers means that there is a proportional decrease in concentration of capillaries per unit area of muscle. Physiologically, however, *it does not seem that the hypertrophied* heart is supplied with insufficient blood. Dock (1941) perfused human hearts postmortem with kerosene and found that the coronary flow is decreased in hypertrophied hearts but found no evidence that the hypertrophied heart has an inadequate blood supply or that its fibers are too thick for adequate oxygen diffusion In addition, the work of Harrison and Wood (1949) indicates that the capacity *of the coronary arteries is directly related* to the weight of the heart and that the cross-sectional area of the coronary arteries increases in hypertrophied hearts They believe that the coronary enlargement keeps pace with the needs of the enlarged heart and that relative ischemia is not a cause of heart failure in hypertension

In atrophic hearts, the muscle fibers have a diminished diameter and their number may be decreased (Karsner *et al.,* 1925), *consequently the capillary concentration* is increased

Development of Collateral Anastomotic Channels. There is abundant experimental and anatomic evidence that partial or complete occlusion of a coronary artery is followed by enlargement of pre-existing anastomotic vessels and development of new anastomotic channels, which then help to supply the anemic or ischemic area with blood. Leary and Wearn (1930) reported two cases *of complete occlusion of* both coronary ostia by syphilis (in patients *aged 35 and 26) and explained the ability* of these patients to live and work, by the development of compensatory circulation

through the thebesian veins. Wiggers (1936) enumerated three types of compensatory anastomoses that may develop after nonfatal coronary occlusion: (1) new intercoronary communications; (2) extracardiac (pericardial) communications, and (3) enlargement of arteriolumınal channels In atherosclerotic occlusion, or in occlusion of the ostium of one coronary by syphilis, new communications of the first type apparently are of most importance, however, in gradual occlusion of both ostia by syphilis, or of the lumina of both vessels near their ostia by atherosclerosis, life may be maintained by development of the last two types of channels named. The new or enlarged channels may serve to prevent death after a subsequent closure of the same vessel or of another branch (Gregg and Mautz, 1938, Blumgart *et al*, 1942). The patient is thus better able to withstand the effects of a gradual occlusion of a coronary artery than the effects of sudden occlusion.

Hudson and associates (1932), by an injection technic, found widespread anastomoses of atrial branches and coronary branches to the pericardial fat with the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta The anastomoses between the cardiac and extracardiac vessels were most extensive around the ostia of the pulmonary veins.

Saphir and associates (1935) found that whenever a myocardial infarct was encountered, at least two branches of the coronary arteries supplying the infarcted area were involved; complete occlusion of two of the three major divisions of the coronary arteries was found in 11 of 30 infarcted hearts studied.

By means of a multicolored injection technic, Schlesinger (1938) demonstrated a rich anastomotic circulation *only* in those hearts in which there was occlusion of the coronary artery; the compensatory blood usually came from the left ventricle. He concluded that anastomoses develop in the coronary arterial system only when and where there is need for them. He found occlusions of two main divisions of the coronary arteries in four of six infarcted hearts. More important than the multiplicity of such lesions is the speed of occurrence of occlusion or narrowing, since a rapid occlusion of one branch will usually result in infarction, even though other branches are normal. Anastomoses, therefore, develop not as a result of aging, but in response to disease of the heart, particularly in atherosclerotic coronary disease.

Blum and associates (1938) gradually occluded the anterior descending branch of the left coronary artery at one point, in dogs, until occlusion became complete at the end of five weeks. The resulting collateral circulation was sufficient to prevent a large part of the myocardial damage which occurred if the same artery was suddenly occluded at the same point. Feil and Beck (1941) operated upon 30 patients to produce vascular grafts on the heart for the purpose of producing a collateral blood supply to the heart. There was improvement in 13 of the 20 who survived. These results were regarded as encouraging, since all of the patients before operation were seriously disabled.

By means of an injection technic, Blumgart and associates (1940) studied the coronary anastomotic circulation. They found no intercoronary anastomoses larger than 40 micra in diameter in normal hearts. In hearts with obstruction to the coronary blood flow by arteriosclerotic narrowing or occlusion, they regularly demonstrated intercoronary anastomoses, measuring 40 to 200 micra in diameter.

Holyoke (1945) applied Schlesinger's technic of injection in 70 hearts and dem-

onstrated a total of 31 points of occlusion of the coronary arteries in 12 hearts. Interarterial anastomoses were found in all *hearts with pronounced arteriosclerotic* narrowing, but in other hearts only in association with marked hypertrophy. Ravin and Geever (1946) also employed Schlesinger's technic in 166 hearts and found *interarterial anastomoses in 36 hearts* Eighteen hearts showed coronary occlusion, in 13 there were associated infarcts, in five no infarcts. Two hearts had infarcts but no occlusion

Prinzmetal and associates (1947) *dem*onstrated anastomotic vessels between the two ventricles by perfusion of the heart postmortem, through one of the branches of the left coronary artery, with radioactive *phosphorus bound to erythrocytes*, and by injection of one of the coronaries with glass spheres of known size. The anastomoses between the intercoronary arteries measured from 70 to 180 micra in diameter, the arteriovenous anastomoses ranged from 70 to 170 micra, and the anastomotic channels between coronaries and the ventricular cavities measured from 70 to 220 micra. Any one or all of these routes of collateral circulation may function following coronary occlusion, and may be a factor in limiting the size of myocardial infarction following obstruction of a major coronary artery. After ligating a coronary artery in the dog, Prinzmetal and associates (1948) perfused the heart with radioactive erythrocytes. They determined that in the left ventricle in the subendocardial portion, the volume of blood in the ischemic myocardium was about two-thirds the *volume of blood in the non-ischemic myo*cardium; while in the subepicardial portion the volume of blood in the ischemic myocardium was equal to that in the adjacent non-ischemic portion. They concluded that *the ischemic myocardium was less well* nourished in the subendocardial portion by collateral circulation, than was the subepicardial portion, thus explaining in myocardial infarction the more extensive *involvement of the subendocardial por*tion than of the subepicardial portion. They also found that, following coronary ligation, both subendocardial and subepicardial portions of the regions of the *right ventricle supplied by the ligated ves*sel contained volumes of blood equal to those in non-ischemic regions of the right ventricle, the ischemic myocardium being normally better nourished by blood through collateral channels than a similar portion of left ventricle. This explains the rarity of infarction of the right ventricle

In summary, when the coronary arteries become narrowed or occluded, the anemic myocardium is supplied by blood from the following collateral sources: thebesian veins, enlarging arterioluminal channels and intercoronary arteries, new intercoronary communications, and new anastomotic channels between the coronary and extracardiac arteries in the pericardial fat

CORONARY SCLEROSIS

Terminology. There is a certain looseness in terminology with reference to de*generative disease of the coronary arteries* Clinically, this may in part be excused, inasmuch as one may not be certain of the exact pathologic lesion present. *Angina pectoris* is a clinical term (see definition, page 201) having reference to cardiac distress, particularly pain or dyspnea, usually of a temporary or transient nature, result*ing from relative myocardial anoxia. This* is usually induced by exertion, eating of meals, excitement and exposure to cold. The commonest pathologic findings in coronary disease are narrowing or occlusion of one or more arteries, old myocardi

fibrosis, stenosis of the coronary ostia resulting from syphilitic arteritis, or cardiac hypertrophy usually of severe degree. Coronary insufficiency (Levy and Bruenn, 1936) and coronary failure are other clinical terms which indicate prolonged functional distress and one may then assume that the myocardium is subject to a relatively severe degree of ischemia. Buchner (1939) and Master and associates (1941) have stressed the condition of *acute coronary insufficiency* which is caused by a deficient supply of oxygenated blood to the myocardium. It is clinically attended by angina, frequently accompanied by transitory electrocardiographic changes (particularly by depression of the ST segment), and often gives rise to focal areas of myocardial necrosis, particularly in the subendocardial layers and the papillary muscles of the left ventricle.

Pathologic terms applying to coronary arterial disease include coronary atheromatosis, sclerosis, atherosclerosis or arteriosclerosis; coronary narrowing, coronary thrombosis, and coronary occlusion; myocardial ischemia, infarction and fibrosis It must be recognized that coronary occlusion and myocardial infarction may exist independently of each other (see pages 576 and 599). Yater and associates (1948a) employed the term "coronary artery disease" for all types of atherosclerotic occlusive disease of the coronary arteries, with or without myocardial infarction. Blumgart and co-workers (1941a) state that the syndrome called "coronary occlusion," consisting of prolonged substernal oppression or pain, a fall in blood pressure, pallor and other manifestations of shock, electrocardiographic changes, fever, leukocytosis and increased sedimentation rate, really signifies myocardial infarction.

The term *atheroma* or *atheromatosis* (of an artery) should indicate a degenerative lesion in which lipoid material, particularly cholesterol, is accumulated in the intima. This condition may be reversible.

The term *atherosclerosis* should be used to indicate the presence, not only of lipoid material and often of calcium as well, but also of reactive connective tissue proliferation. The atheroma may be primary or it may be secondary to the sclerotic changes and may, in part, be reversible.

The designation *arteriosclerosis* has been applied to a variety of diseases of the arteries and arterioles, and it has also been used synonymously with atherosclerosis. It is characterized chiefly by fibrosis or hyalinization and sometimes also by calcification particularly in association with atheromatous deposits, the latter deposits being either primary or secondary to the sclerotic changes Arteriosclerosis frequently develops in association with an area of inflammation and in such cases ordinarily reveals no atheromatous deposits.

In this chapter we shall attempt, whenever possible, to be selective in the use of these terms. When it cannot be determined whether atheromatosis or arteriosclerosis was the primary process in the coronary arterial disease we shall use the term *atherosclerotic coronary disease* or simply *coronary sclerosis.* In this chapter we shall also consider such conditions as coronary thrombosis, intramural hemorrhage of a coronary artery, and myocardial infarction.

The description of atheromatous and atherosclerotic changes in the coronary arteries has been largely taken from the work of Wolkoff (1929). Ehrich and associates (1931) noted that the atherosclerotic changes which Wolkoff described, in general occurred at an earlier age in their subjects in New York City. The atherosclerotic changes in the coronaries are similar to those which occur in the aorta. It must be emphasized, however, that atherosclerotic changes of the arteries vary greatly with respect to their occurrence and severity, in different persons of the same age.

Macroscopic Changes

1. *Atheroma.* The first macroscopic changes occur in the form of yellowish minute (pinhead-sized) spots of lipoid material visible beneath the intima, which are round and scarcely elevated above the surface. They were encountered by Wolkoff as early as the beginning of the second decade (one to three spots in subjects aged 9, 10 and 11 years), and were seen by her in one-half of the subjects during the second decade of life, in two-thirds of those during the third decade of life and in the coronaries of all persons after their fortieth year While Monckeberg found this change earliest in the left coronary artery (at about age 15) and claimed that this was generally the site of earliest localization of atheroma in the body, Wolkoff always found such spots in the aorta above the aortic valve and in the mitral valve earlier than in the coronary arteries. In the second and third decades the spots are more numerous, larger, rounded or oval, or occur as streaks, 1 to 2 cm long, which follow the long axis of the artery. The process, in general, increases in severity with age Its order of localization is as follows: first portion of anterior descending branch, main stem of left coronary, first portion of right coronary, and first portion of left circumflex branch.

Klotz and Manning (1911) encountered fatty streaks in the intima of the aorta most frequently between the ages of 21 and 30 (in 12 of 15 subjects) and rarely (only once in 10 subjects) after the age of 50. They believed that many of these superficial lesions disappeared almost entirely, leaving the artery "in an elastic condition equal to normal"

2 *Fibrous plaques* Beginning at about age 30, the fatty spots, in part or whole, become covered by hyaline-like connective tissue, forming rounded or irregular plaques of white color which encroach upon the lumen. These also make their appearance first in the left coronary, the order of localization being the same as that of the lipoid deposits which precede them.

Fibrous plaques may be encountered without accompanying lipoid deposits and in such cases one may not always be able to determine if the fibrosis was preceded by *lipoid deposits or if it was a primary* change. Indeed, Duguid (1946) is of the opinion that not infrequently coronary thrombosis is followed by fatty degeneration and that fibrosis results from the organization of the clot; in such cases Duguid believes that thrombosis may be a factor in the production of coronary atherosclerosis, rather than a consequence of it.

3. *Calcification.* In later decades, rarely before 40, the plaques become calcified, or they may show ragged ulceration of the intimal surface, frequently with secondary thrombosis. In middle age or later, the main stems and main branches of the coronaries, therefore, frequently show scattered plaques, often with points of narrowing of the lumen, particularly at sites of arterial branching, at such points of constriction, thrombosis is favored. Again there may be more or less diffuse atherosclerosis with thickening and rigidity of the wall, sometimes with calcification. Such rigid vessels often have narrow lumina, at other times the lumina are wider than normal, as a result of loss of elasticity, presumably because of age, and the vessels are tortuous Thus, sclerosis may be focal or diffuse, present with or without narrowing of the lumen, and with partial or complete occlusion.

Microscopic Changes

1. Even before the fatty spots become grossly visible on the intimal surface, lipoid material staining with Sudan III is demonstrable in the deeper layers of the intima. The ground substance in this layer does not then show the pale rose color w l

van Gieson's stain as normally; at these sites the lipoid material is deposited focally, causing separation of the elastic fibers. The deposits of lipid accumulate, causing elevation of the surface of the intima, and they may also encroach upon the media. The lipid also frequently infiltrates the cells of the intima, sometimes those of the media, and occasionally even those of the adventitia

2 As early as age 15, a connective tissue layer is demonstrable in the intimal zone on the inner aspect of the hyperplastic layer at sites of foci of lipoid material Some of these connective tissue cells may be infiltrated with lipid Bork (1926) found that comparable changes did not develop in the aorta until age 25 and in the femoral artery until 40 years of age.

3 In some subjects, as early as age 20, the lipoid foci are associated with, or converted into, plaques of fibrous or hyaline connective tissue and some of the lipoid material may be resorbed (Klotz and Manning, 1911, Anitschkow, 1933) The fibrous plaques occur on the inner aspect of the elastic-hyperplastic layer and consist of wide bands of hyalinizing fibers which stain bright red with van Gieson's method. At times these hyaline fibers may surround a focus of fatty material. The fibro-lipoid plaques may become exceedingly thick, even up to 10 or 20 times the thickness of the media They may encroach upon the lumen and even occlude it, but the general structure of the musculoelastic and of the elastic-hyperplastic layer is usually maintained. The lipoid foci and the fibrous plaques may stretch the elastic fibers of the media and may cause atrophy of this layer.

4. In *advanced cases* of atheromatous deposits, one may encounter cholesterol crystals which are surrounded by other lipoid material or are present within the fibrous tissue of a plaque. The intima may become ulcerated and the seat of thrombi. In large fatty foci or in fibrous plaques, calcium may be deposited, as early as age 40, occasionally ossification may occur, usually at sites of previous calcification.

5. In about one-half of cases, beginning at age 40, there is ingrowth of blood capillaries into the atherosclerotic plaques. In advanced coronary sclerosis, such vascularization is constantly present (Leary, 1938). These vessels come principally from the vasa vasorum in the adventitia and outer half of the media and in rare instances they spring directly from the lumen of the coronary artery, apparently by proliferation of the intimal endothelium Newly formed capillaries are bordered by lipoid macrophages There is also usually associated an infiltration of lymphoid cells (Figure VII-4), principally in the adventitia, but also in the media and even in the intima The infiltration is often perivascular. The adventitia becomes thicker and more fibrous. Sometimes the capillaries rupture and the resulting hemorrhage may extend to the lumen and lead to formation of an obstructing thrombus.

All of the above changes appear to be but different stages in the process of atherosclerosis. It must be noted, however, that many of the atherosclerotic changes in the intima occur concomitantly with changes which are attributable to age.

In the presence of atherosclerosis of the larger coronary vessels, the small intramuscular branches may show similar mild lesions but in most instances they are entirely free from such changes.

Grading of Coronary Sclerosis. Table VII-1 lists the principal microscopic features in early, moderate and advanced (grades 1, 2 and 3) coronary sclerosis, based on the findings of Yater and associates (1948c).

Vascularization of the Intima of the Coronaries. A number of investigators (Wolkoff, 1929, Leary, 1934; Paterson, 1936; Winternitz *et al.*, 1937; Wartman,

Table VII-1
Grading of Coronary Sclerosis
(After Yater *et al*, 1948c)

Pathologic Feature	*Degree of Atherosclerosis*		
	Grade 1 Early	*Grade 2 Moderately Advanced*	*Grade 3. Advanced*
I Atheromatous plaque			
1 Connective tissue	Loose, young fibroblasts	Hyalinized at base	Hyalinized at base and surface
2 Amorphous material	Little or none	Much cholesterol or lipid	Much cholesterol or lipid
3 Cholesterol	Few or no crystals	Few clefts	Many clefts
4 Vascularization	Slight or none	Slight, marginal	Abundant, marginal and basal
5 Calcium	None	Minimal	In masses
II Internal elastic lamina	Slight to moderate damage	Fragmented or absent	Severely damaged or absent
III Media beneath plaque			
1 Thinning	Slight	Moderate	Media atrophic
2 Loss of muscle fibers	Little or none	Moderate	Moderate
3 Fibrosis	Minimal	Increased	Increased, hyalinization

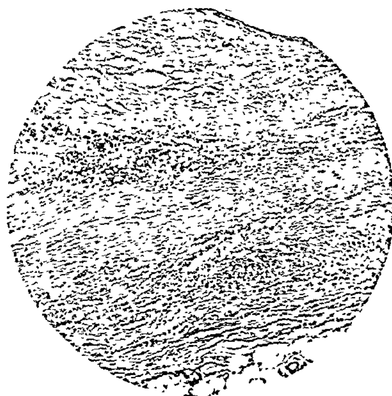


Figure VII-4 Portion of wall of atherosclerotic coronary artery, showing organization of intima in association with lipid material, and in deeper portion of media X 150. (WCGH, 40 A 460)

1938) have observed capillaries apparently arising from the intimal endothelium of an atherosclerotic coronary artery, with or without thrombosis. Paterson found such vascularization of the intima to be common in thrombosis of coronary arteries

Localization of Coronary Sclerosis. The localization of atherosclerosis in the coronaries is earliest and most severe in the first portion of the anterior descending branch of the left coronary and in the main stem of the left coronary artery; next, in the first portion of the right coronary artery and then in the first portion of the left circumflex branch. In only five of 120 hearts studied by Wolkoff (1929) were atherosclerotic changes more severe in the right coronary than in the left, and in four of these the left circumflex branch was poorly developed and its function largely taken over by the right coronary Atheromatous foci also are seen particularly on the wall of the artery which lies adjacent to the myocardium rather than on the wall of the artery which lies adjacent to the epicardium; such foci are also prominent in the main vessels at sites of branching. According to Geiringer (1951), however, atheroma rarely occurs in stretches of the anterior descending coronary artery which are covered by myocardium. Geiringer found that this vessel is covered in part or all of its course by myocardium in approximately one-fifth of human hearts and designated such arteries as "mural" coronaries.

Sclerosis of the coronaries generally precedes sclerosis of other arteries of the body. In men under 40, Dock (1946) found that coronary sclerosis was usually not associated with sclerosis of the aorta or cerebral or tibial arteries. Munck (1946) compared the degree of atherosclerotic changes in the coronaries, aorta and cerebral arteries in 396 persons who died suddenly from the effects of coronary sclerosis. He found that sclerotic changes in the left anterior descending branch were relatively more advanced than in the aorta or the arteries of the brain.

In an analysis of the gross pathologic findings in 80 fatal cases of coronary atherosclerosis among soldiers 20 to 36 years of age, French and Dock (1944) found atherosclerotic lesions present in more than one of the main coronary branches in 67 hearts The most important stenosing lesion was found in the anterior descending branch of the left coronary in 63 hearts, in the right coronary artery in 11 hearts and in the circumflex branch of the left coronary in 6 hearts.

White and associates (1950) sectioned the coronary arteries and their main branches at intervals of 3 mm., and measured the degree of sclerosis, in the hearts of 100 men in each decade between the ages of 30 and 89. Ackerman and coworkers (1950) made a similar study of the hearts of 100 women in each of these six decades. In both studies, in nearly every decade, the degree of sclerosis was greatest in the anterior descending branch of the left coronary, and less severe in the following arteries in the order named: right main coronary, left circumflex branch, stem of left coronary, right posterior descending and right marginal branch. As a rule, the degree of sclerosis in each of the six vessels examined was greatest in the proximal third, less in the middle third and least in the distal third.

The greater involvement of the anterior descending branch by atherosclerosis may possibly be related to a relatively greater traumatizing effect of the blood which flows at an angle of approximately 180 degrees to that of the ascending aorta as compared to the right coronary artery and the left circumflex branch in both of which vessels the blood flows approximately at right angles to that of the aorta.

Etiology and Pathogenesis

Incidence and Severity of Coronary Sclerosis in Relation to Age and Sex. With the increasing control of many infectious and neoplastic diseases and the consequent increasing span of human life, an increasing incidence of coronary sclerosis is apparent.

Rossle (1919, quoted by Karsner, 1933) found that among soldiers in World War I, the incidence of coronary sclerosis at autopsy rose steadily from 10.6 per cent in the age period 15 to 20, to 50 per cent during the period 45 to 50. Levy and associates (1934) found lesions of coronary arteries in 25 9 per cent of 2877 consecutive autopsies. In one-half of these autopsies, the lesions were slight or moderate, in one-half severe Coronary sclerosis was present in 19 per cent of persons in the age group 25 to 44; in 40 per cent in the group 45 to 60, and in 60 per cent past 65 years. In an analysis of 476 cases at autopsy, severe coronary disease was approximately three times as common in men as in women (Bruenn *et al.*, 1936). Gordon and associates (1939) in a study of 3400 consecutive autopsies found a steady increase with age periods in the incidence of coronary sclerosis (a) without narrowing, (b) with narrowing, (c) with partial occlusion, and (d) with occlusion. Clawson (1941) reviewed the protocols of 30,265 autopsies and determined that in 4678 subjects death was attributed to heart disease. Among these 4678 subjects, coronary sclerosis was present in 25 9 per cent. Willius and associates (1933) reviewed protocols of 5060 consecutive autopsies and found that coronary sclerosis increased steadily with age in both sexes. Among 188 female subjects in the first decade the heart in 92 per cent showed no sclerosis and the remaining 8 per cent had only grade 1 sclerosis, while all 78 subjects aged 70 or over showed some sclerosis, in most cases of moderate or severe degree. In the eighth decade 3 per cent had grade 4 sclerosis and in the ninth decade, 11 per cent had grade 4 sclerosis.

White and associates (1950), in their study of cross sections at 3-mm. intervals of the coronary arteries of 100 hearts of men from each decade between the ages of 30 to 89 inclusive, found the greatest degree of sclerosis in each of the six branches occurred in the decade 50 to 59, at which period 75 per cent of hearts showed severe sclerosis of one or both coronary arteries In the age period 30 to 39, 18 per cent of hearts had, at some site, sclerosis of grade 3 or 4 (on the basis of 0 to 4), and beyond age 49, most men had grade 3 sclerosis at some point in either or both coronaries. The average grade of sclerosis increased with age, from decade 30 to 39 to a maximum in decade 50 to 59 and thereafter decreased somewhat.

Ackerman and associates (1950), who made a similar study of 600 hearts of women, found that the severity of sclerosis increased for each decade to a maximum in the eighth and ninth decades, when 60 per cent of hearts showed severe coronary sclerosis (grade 3 or 4) at some point in either coronary or in both coronaries.

A comparison of the findings in these two series indicates that coronary atherosclerosis is more severe in men, especially before the age of 60.

As one would expect, in younger patients with fatal coronary insufficiency, solid cellular xanthomatous plaques are more frequent (French and Dock, 1944) and calcification is less frequent (Moritz and Zamcheck, 1946). Leary (1936) has drawn a distinction in the evolution of the atherosclerotic lesion at different age periods. In youth the lipoid deposits are converted into fibrotic lesions with minimal scarring, and if the lumen becomes occluded it is due to thrombosis whi

follows necrosis of the subendothelial layer and endothelium, in middle age the connective tissue forms collagen and scar tissue, while in old age the lipoid accumulations, having minimal fibrous tissue support, rupture and thus lead to thrombosis. The incidence of coronary artery disease is far greater among men. Master (1947) determined that coronary artery disease was three times as frequent among men as among women, Levy and Boas (1936), 4 8 times as frequent.

Coronary Arterial Disease in Infants and Children. Clinically significant atherosclerosis of the coronary arteries, so commonly encountered in adults, is decidedly rare in infants and children

The youngest patient reported to have died of coronary occlusion by atherosclerosis (Jokl and Greenstein, 1944) apparently was a 10-year-old boy The left descending branch was almost completely occluded by an organized thrombus for a distance of about an inch, beginning one-half inch from the orifice of the vessel Five other instances of sudden death from coronary arteriosclerosis in children, ranging from 12 to 15 years of age, are listed by Rigdon and Willeford (1950).

The commonest lesion of the coronary arteries encountered in infants and children is termed *medial coronary sclerosis* (Brown and Richter, 1941) or medial calcification with fibroblastic proliferation of the intima (Stryker, 1946a). Brown and Richter found the calcification to affect the internal elastica chiefly. With the calcification there is frequently a coexisting internal fibroblastic proliferation which may lead to occlusion of the vessel. They suggested that a disturbance of calcium and phosphorus metabolism may be at fault.

Stryker reported four such cases and refers to 15 others (seven male and eight female) in the literature in which the ages ranged from 1 day to 27 months. One of Stryker's patients was an infant, aged three months, who had complete occlusion of one coronary artery, except for small foci of recanalization, and small areas of recent myocardial infarction. Stryker (1946b) found the calcification to affect the region of the internal elastic layer, sometimes being present on both sides of this layer, but having a greater tendency to affect the wall on its internal aspect. In each of five subjects, arteries in other organs of the body were similarly involved. He points out that this condition is to be distinguished from Monckeberg's sclerosis in which calcific deposit lies in the media proper and is limited by the internal elastic lamina.

Other causes of occlusive disease of the coronaries in infancy and childhood include rheumatic arteritis, polyarteritis (periarteritis) nodosa (Sinclair and Nitsch, 1949), and embolism, chiefly from bacterial endocarditis, and more rarely, congenital abnormalities, hypertension and syphilitic arteritis

Race. Most American writers who have statistically analyzed the racial incidence of coronary arteriosclerosis, coronary thrombosis and myocardial infarction, as checked at autopsy, find that these conditions are less common in Negroes than in white persons. (See Hedley, 1935, 1939, Fitzgerald and Yater, 1946, Moritz and Zamcheck, 1946; Yater *et al.*, 1948a.) On the other hand, it is generally recognized that among Negroes there is a higher incidence of essential hypertension and of syphilitic aortitis and its complications, and that death from these causes is relatively more frequent than in white persons. Furthermore, the average age at death among Negroes is lower than that of white persons. Thus in 1947, among policy-holders of the Metropolitan Life Insurance Company, the mortality of colored men at ages 20 to 35 was at least 1⅓ times that of white men; for colored women at ages 15 to 25, more than three times that of white women; and from age 30 to 45 more than

double the rate for white women (*Statistical Bulletin*, Aug. 1948). The expectancy of life at birth in 1949 in the United States was as follows. white males 65.88 years, nonwhite males 58.57 or a difference of 7.31 years in favor of white males, white females, 71.51 years, nonwhite females 62.93 or a difference of 8 58 years in favor of white females (*Statistical Bulletin*, Nov. 1951).

Bruenn, Turner and Levy (1936) in their series of patients with coronary sclerosis found a ratio of white to colored patients of 12 to 1. They thought that angina was rare in the colored race probably, in part, because of the rarity of advanced sclerosis in the Negro. Blache and Handler (1950) found that the incidence of coronary thrombosis at autopsy among 2963 Negroes was only 1.1 per cent as compared to 17.9 per cent among 1961 white persons. They studied segments of the coronary arteries by staining of elastic tissue and by microincineration, and concluded that the rate of development of coronary arteriosclerosis in the Negro lags behind that of the white person by approximately a decade, for the fourth to sixth decades inclusive. They related this lower incidence to a greater tendency of the elastic tissue of the coronary arteries to swell but a lesser tendency to fragment and calcify.

The statement that arteriosclerosis is less frequent among Chinese than among persons of the white race apparently has not been proved as yet (Weiss and Minot, 1933b, Gertler *et al*, 1950b).

Familial Tendency. The tendency to develop coronary sclerosis may be familial (Ophuls, 1933b, Bean, 1937).

Sudden death, presumably from coronary disease, was reported as occurring in a man at age 42 and three of his sons, at ages 43, 30 and 31 (Herapath and Perry. 1930). The oldest son and one of the younger sons came to autopsy and their coronary arteries showed gross atheromatous changes. In the heart of the oldest son, the gross diagnosis was confirmed by microscopic examination Fatal coronary disease in homologous twins was reported by Froment and associates (1945). Both developed severe angina pectoris at the age of 34. One twin died at age 35 and at autopsy showed severe atheromatous disease of the coronary arteries with diffuse myocardial degenerative changes. The other twin died suddenly in a spontaneous attack three years later. No autopsy was performed but an electrocardiogram two years before death confirmed the clinical diagnosis of coronary disease

Yater and associates (1948c) believed that heredity may be an important factor in the development of coronary artery disease in soldiers under the age of 40, since hypertension and/or coronary artery disease occurred in other members of the immediate families of 41 per cent of soldiers who survived an attack of myocardial infarction as compared with an incidence of 13 per cent in families in a control group of soldiers.

Xanthoma tuberosum, an inherited disturbance in metabolism of cholesterol, is manifested by hypercholesterolemia and by xanthomatous plaques in the subcutis of the extensor surfaces of the extremities and in various organs including the aorta and coronary arteries As a result of the xanthomatous deposits in the coronary arteries, these subjects are predisposed to sudden and often premature death from coronary occlusion

Rigdon and Willeford (1950) reported sudden death in a boy of 12 At autopsy both coronaries showed narrowing of the orifices and decided decrease of the lumina by atheromatous plaques in the first 2 or 3 cm.; this process was particularly severe in the first portion of the anterior descending branch. In [illegible] atheromatous plaques [illegible]

aorta, innominate, left carotid and left subclavian arteries, and on the mitral valve The myocardium showed extensive myocardial degeneration but no definite area of infarction. These authors also summarized the findings in two other reported cases of xanthoma tuberosum in children One was a boy 13 years of age with severe aortic and coronary arteriosclerosis with pronounced narrowing of the anterior descending vessel and an infarct of the ventral wall of the left ventricle. The other child was a girl 11 years of age.

In an instance of xanthoma tuberosum that came to my attention, the subject was a boy eight years of age. He had previously had no cardiac complaints. On the day before death he collapsed after walking four blocks in the snow At autopsy, performed two hours after death, the cholesterol content of the heart's blood was 1000 mg. per 100 ml. In addition to the cutaneous manifestations (Figure VII-5), he showed xanthomatous plaques with narrowing of the coronary arteries and almost complete occlusion of the right coronary artery at a point 4 mm. from its orifice. Large plaques were present throughout the aorta but especially in the ascending thoracic portion (Figure VII-6), *the entire circumference of the first 3 cm.* of the vessel being involved. Gross xanthomatous infiltrations were seen in the mitral and aortic valves and the endocardium adjacent to these valves; in the ring of the pulmonary valve and the intima of the pulmonary trunk in the region of the commissures of the cusps of this valve; in the mediastinal and mesenteric lymph nodes and in the renal pyramids. There was no gross or microscopic evidence of myocardial infarction. Section of the wall of the coronary artery revealed changes which were similar to those of the atherosclerosis seen in adults. These consisted of deposits of lipoid material, severe thickening by connective tissue which was undergoing hyalinization, formation of new capillaries, and a mild degree of lymphocytic infiltration (Figure VII-7). There was some atrophy of the media.

Body Build and Weight in Coronary Sclerosis. Levine and Brown (1929) believed that thin persons have less tendency to coronary sclerosis than obese persons. According to Dublin (1930), this belief is confirmed by insurance tables which show higher death rates among overweight persons for each of the following categories of diseases: organic diseases of the heart, angina pectoris and diseases of the arteries. Underweight persons have lower rates than persons of normal weight. Bähr (1938), in a study based on 308 autopsies, also found coronary sclerosis more frequently among florid and robust persons than among asthenic persons. On the other hand, Bean (1937) did not find such a correlation in his study of 300 cases of myocardial infarction; the age of onset did not vary significantly in persons of thin, normal or obese build. Moritz and Zamcheck (1946) did not find obesity to be a significant factor among soldiers under 40 who died suddenly and unexpectedly from coronary disease. Similarly, Yater and associates (1948a) studied the *autopsy records of 450 soldiers* under the age of 40 who died from coronary artery disease, and found that obesity was not a factor of any importance.

Faber and Lund (1949) studied the influence of obesity on arteriosclerotic changes in 408 aortas. They determined the dry weight of the aorta after removing the adventitia, and obtained the content of cholesterol and calcium. They found that hypertension gives a rise in the content of these substances greater than would be expected for the given age but that obesity, in itself, has no effect upon their content.

Incidence of Coronary Artery Disease According to Occupation. It may be stated

Figure VII-5 Skin lesions of xanthoma tuberosum in boy eight years of age (WCGH, 49 A 460)



Figure VII-6 Large atherosclerotic plaque of aorta in boy of eight years with xanthoma tuberosum Death was caused by coronary insufficiency The right coronary artery was almost completely occluded by atherosclerosis (W[illegible] A 460)

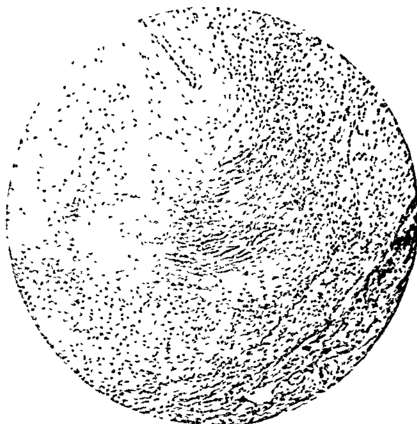


Figure VII-7 Segment of cross section of right coronary artery in boy with xanthoma tuberosum Considerable connective tissue thickening and hyalinization of intima, with some cholesterol deposit X 100. (WCGH, 49 A 460)

that, in general, occupation does not seem to be an important factor in the causation of coronary sclerosis.

Bruenn and associates (1936) determined that cardiac pain occurred more often among housewives (29 per cent) and manual workers (28 per cent) than among professional workers and executives (only 18 per cent) Bahr (1938), in his study of 308 autopsies, encountered more involvement of coronaries among subjects who were "white collar" and professional workers than among those who were manual workers. An inquiry by Yater and coworkers (1948a) into the case histories of soldiers who died suddenly of coronary artery disease revealed a higher incidence among those who had been engaged in physically less arduous occupations, such as clerical, professional and supervisory, than among laborers and farm or factory workers Levine and Hindle (1945) found no significant difference between physicians and the general population in the average age of death from coronary disease.

Coronary Occlusion in Animals. An instance of coronary thrombosis in an eight-year-old female ape was described by Manning (1942). The clinical signs, manner of death and pathologic changes were comparable to those in coronary thrombosis in man. Crosfield (1944) reported the occurrence of coronary thrombosis in a three-year-old Ayrshire bull; and Gilyard (1944) reported thrombotic occlusion of the middle third of the right coronary artery in a six-year-old West Indian-bred thoroughbred gelding which collapsed after completing a race of one mile and one hundred thirty yards. Highman and Altland (1949) found thrombotic coronary

occlusions and extensive myocardial infarction in one of their rats that died after exposure to an altitude of 25,000 feet for four hours daily.

Seasonal Incidence of Coronary Occlusion. In the north temperate regions of the United States attacks of coronary occlusion are found to occur more frequently during the cold winter months than during the warm summer months. This occurrence is probably to be related to the greater metabolic activity of the body and the greater frequency of respiratory infections during the cold months. Bean and Mills (1938) found that the incidence of cardiac failure from rheumatic disease and arteriosclerosis also showed a similar seasonal variation, probably for the same reasons.

Morbidity and Mortality of Coronary Artery Disease in the United States. In a statistical study of mortality from heart disease among white persons in the United States in 1940, Gover and Pennell (1950) found that the principal type of heart disease causing death at various age periods was as follows. under five years of age, congenital heart disease, from five to 35 years, valvular heart disease; from 35 to 65 years, diseases of the coronary arteries, and over 65 years, diseases of the myocardium. Undoubtedly most cases in this last category actually represent diseases of the coronary arteries

Master (1947) estimated that there were 120,000 deaths from acute coronary occlusion in the United States in 1942 The increased number of reported deaths from this condition in recent years has been attributed to. (1) lengthened span of life; (2) aging of the population, (3) improved diagnosis and treatment, and (4) increased accuracy in terminology.

In 1949 (see *Vital Statistics*, 1951) diseases of the heart were responsible for 518,568 deaths in the United States (exclusive of fetal deaths and of deaths among armed forces overseas), cancer, the second leading cause of death, was responsible for 206,325 deaths Among the diseases of the heart, arteriosclerotic heart disease, including coronary diseases, caused 299,109 deaths. In addition, there were 34,648 deaths listed in the category, "other myocardial degeneration, with arteriosclerosis," making a total of 333,757 deaths attributed to arteriosclerotic or coronary heart disease. Inasmuch as nearly all coronary disease is arteriosclerotic in etiology, there can be little doubt that arteriosclerotic disease of the coronary arteries is now the leading cause of death in the United States. Furthermore, in recent years, along with the extension of the average life expectancy at birth, the total number of persons and the percentage of those who die of diseases of the heart, and particularly of the effects of coronary sclerosis, have been constantly increasing. During recent years, therefore, increasing attention has been directed to the etiology and control of arteriosclerosis and coronary occlusion

Master and associates (1939c) estimated the number of attacks of coronary occlusion that occur annually at 1,000,000 while Friedberg (1949) placed this number at about 500,000 McCain and associates (1950) found myocardial infarcts in 7.8 per cent of 3559 autopsies in Cleveland. If we assume that approximately the same percentage of myocardial infarcts occurs among the total number of over 1,500,000 deaths annually in the United States, myocardial infarcts will be found in approximately 120,000 persons at autopsy, and if the average length of life following the first attack of myocardial infarction is taken as five years (Katz *et al.*, 1949), then there are now approximately 600,000 persons living in the United States who have had one or more infarctions.

Pathogenesis of Atheromatosis. Of the

various theories of origin of atheromatosis, the imbibition theory of Virchow seems most plausible This attributes the deposition of lipids in the intima directly from the lumen of the vessel by infiltration from the plasma. It must be admitted, however, that the correlation between concentration of blood lipids and degree of atheroma is none too good

Leary (1941) believes that lipid-carrying macrophages are attracted to the intima by a process of chemotaxis, penetrate the endothelium and deposit the lipoid material in the intima. The general opinion, however, holds that lipids are deposited in the intima before the lipophages appear. Winternitz and associates (1938) attributed the primary change to hemorrhage from rupture of new capillaries that arise from the vasa vasorum or directly from the lumen. Generally, however, hemorrhage is not found in association with atherosclerosis; when it does occur, it probably does not precede but rather follows the onset of atherosclerosis. With increasing age, there is an accumulation in the intima of lipids which are precipitated in the ground or cement substance, with the formation of cholesterol crystals Later, fibrous proliferation with or without scarring, vascularization, inflammatory cell infiltration or calcification may occur

Hueper (1942) injected various macromolecular compounds, including proteins, carbohydrates and lipins, into animals and produced which are comparable to choles- lesions. He believes that these substances cannot be broken down or excreted by the body and that as a result of disturbances in nutritive and oxidative metabolism of the vascular walls, degenerative lesions are produced which are comparable to cholesterol atheromatosis of man.

As previously mentioned (page 557), Duguid (1946) has presented evidence that coronary thrombosis may be followed by fatty degeneration in the thrombus. He believes that such thrombosis may actually be a factor in causing coronary atherosclerosis.

Only a few factors in the pathogenesis of atheromatosis in man are known. The relationships of this process to the metabolism of cholesterol, to the intake of lipids in the diet, cholesterol "antagonists" (iodides, thyroid extract, choline, lecithin), or alcohol, to infections and wasting diseases, to age and local trauma, to heredity, bodily build and weight, to occupation, emotional factors, hypertension, preexisting local disease, and to endocrinal and metabolic diseases, are only partially understood. For review of literature on Arteriosclerosis, see Hueper (1942).

Hirsch and Weinhouse (1943) believe that with age there is a significant increase in the media of the free and total cholesterol, phospholipids, galactosides and glycerides, and a marked increase of the calcium content; these changes apparently are related to age and do not cause atherosclerosis. The lipids of the intima seem to originate in the plasma rather than in the protoplasm of the cells. Most cases of atherosclerosis in man are not accompanied by hypercholesteremia Undoubtedly some changes incident to age occur in the tissues of blood vessels which lead to the deposition of the lipids.

According to Katz and Dauber (1945), it appears that *elevated serum cholesterol* favors atherosclerosis but is not essential for its occurrence; that potassium iodide, with the help of the thyroid gland, may prevent experimental atherosclerosis which results from cholesterol feeding, but will not remove lesions produced by earlier cholesterol administration, and that the results of administration of choline and lecithin in preventing hypercholesterolemia and atherosclerosis or in favoring the resorption of atheromatous lesions are variable. Boas and associates (1948) believe

that the frequent hypercholesterolemia in patients with coronary arteriosclerosis suggests an etiologic relationship.

Gertler and associates (1950a) determined the serum cholesterol concentration in 146 healthy men and in 95 men who had had a myocardial infarct before the age of 40. Those with coronary artery disease had markedly higher serum cholesterol levels than the healthy persons, and in both health and coronary disease the level of serum phospholipids was highly correlated with that of the serum cholesterol. They believe that the levels of serum cholesterol and serum phospholipids are less important in coronary artery disease than is the ratio of cholesterol and phospholipids.

Leary (1931) maintains that *alcoholism* is associated with absence of arteriosclerotic changes in the aorta. Eberhard (1936) studied the effect of alcohol on the development of atherosclerosis in rabbits. He fed alcohol alone, cholesterol alone and both alcohol and cholesterol, each to groups of five rabbits. Animals fed alcohol showed an increase in the cholesterol level compared to the control group, and animals fed both alcohol and cholesterol showed an increase in the cholesterol blood level compared to those fed cholesterol alone. At the end of the experiment the cholesterol content of the liver and aorta of the animals fed alcohol alone was lower than in the control animals, and the cholesterol content in the liver and aorta of the animals fed both alcohol and cholesterol was lower than in those fed cholesterol alone. These findings suggest that alcohol may interfere with the development of atherosclerosis in the aorta. Wilens (1947a), however, believes that in man the habitual use of alcohol does not have any appreciable effect on production of atherosclerosis.

There is no proof that *overnutrition* is responsible for arteriosclerosis in man (Weiss and Minot, 1933a). While obesity and arteriosclerosis are often associated, the arteries of obese persons past 50 may be unusually free of sclerosis. In diabetics, on the other hand, it is generally conceded that arteriosclerosis (or atheromatosis) occurs earlier than in nondiabetics and is usually more severe in degree than in nondiabetics of the same age. In diabetes and in multiple xanthomatosis, myxedema and lipoid nephrosis, the associated high lipemia and cholesterolemia are often to be related to the development of atheromatosis and to be attributed to an endogenous fault in metabolism. Neither has it been proved that a relatively high protein or a relatively high carbohydrate diet is either responsible for, or prevents the development of, atheromatosis or arteriosclerosis; or that a vegetarian diet tends to prevent the development of atheromatosis. Wilens (1947b) found severe atherosclerosis of the coronary arteries in 12 of 24 obese patients aged 40 to 60 years, and in only two of 39 poorly nourished persons in the same age group According to Gertler and coworkers (1950b), the level of serum cholestrol is independent of dietary cholesterol within normal limits of digestion and the concentration of serum cholesterol is mainly dependent upon the balance between synthesis and utilization. These observers believe that there is no advantage to be gained from imposing a low cholesterol diet on patients with coronary artery disease

Bahr's (1938) subjects with cancer or tuberculosis had delicate coronary vessels and Wilens (1947b) found evidence that atherosclerotic lesions are less severe in wasting diseases such as cancer and advanced tuberculosis. Persons past 50 having advanced tuberculosis or cachexia of cancer frequently reveal surprisingly little arteriosclerosis. It is possible that in these conditions the body has metabolized (either more completely utilized or resorbed)

cholesterol material that previously was deposited in the arteries Wells (1933) pointed out that extensive lipid infiltration of the aorta in youth commonly disappears without leading to atherosclerosis (see also Klotz and Manning, 1911), while sclerotic patches may be found free from lipids Since it appears that the deposition of atheromatous material in the intima is reversible, it should be possible, within limits, to inhibit the formation of atherosclerosis.

Morrison and Gonzalez (1950) administered choline, a lipotropic substance, for periods of one to three years, to 115 patients with clinically proved myocardial infarction They believe that in this group the subsequent mortality rate was significantly reduced as compared with that of a comparable control group of patients

Summary of Factors in Arteriosclerosis. It appears that there are a number of factors which operate in causing arteriosclerosis. These include mechanical factors (increased intravascular pressure as in lower abdominal aorta, eddying of stream at sites of branching of arteries), ingestion of substances which are not completely metabolized (macromolecular substances) and local degenerative changes resulting from previous infection (arteriosclerosis superimposed on syphilitic aortitis) and involution.

Causes of Coronary Occlusion. The principal cause of coronary occlusion is atherosclerosis with or without superimposed thrombosis The ostium of either main coronary artery may be occluded by syphilitic arteritis as an extension of the disease from the aorta. Occasionally a coronary artery may be occluded by embolism, polyarteritis nodosa, thromboangiitis obliterans, rheumatic infection, mycotic infection or as a result of trauma. These subjects are discussed in some detail in other sections. Occlusion may also be caused by pressure from without, as by neoplasm, extension of a dissecting aneurysm of the aorta (Bayley and Monte, 1943) or aneurysm of the sinus of Valsalva (Chipps, 1941).

Coronary Artery Disease in Diabetes Mellitus. Among diabetics over the age of 40, coronary sclerosis, angina pectoris and death from coronary disease are as common in women as in men, but in nondiabetics these conditions are much commoner in men(Stearns *et al.*, 1947) These authors state that any diabetic of either sex over the age of 40 can be assumed to have severe coronary sclerosis, especially if he also has hypertension or if his diabetes is of 10 or more years' duration. The severity of vascular disease in the diabetic is related to the duration and degree of control of the diabetes (Root, 1948).

Nathanson (1932) found severe coronary sclerosis in 41 of 100 autopsied diabetics (and in 53 per cent of diabetics above the age of 50), as compared with 8 per cent of 250 nondiabetic subjects in the same age group. In nondiabetics the ratio of males to females was 3 to 1, in the diabetic series 1 8 to 1.

The diabetic not only has a more severe degree of arteriosclerosis (atherosclerosis), but develops arteriosclerotic (atherosclerotic) lesions ten or twelve years earlier than the nondiabetic (Warren, 1938). Warren found infarcts in 16.4 per cent of the hearts of 440 diabetic patients compared to only 4.1 per cent encountered by Benson and Hunter (1925) in 1750 autopsies, and to 4.9 per cent among 1000 consecutive unselected autopsies studied by Barnes and Ball at the Mayo Clinic.

Blotner (1930) reported death from cardiac infarction in 3 diabetics following a rapid fall in blood sugar after administration of insulin, and called attention to the danger of inducing coronary thrombosis by insulin in the elderly diabetic with vascular disease. Atherosclerosis of the coronary arteries, as well as of the peripheral

arteries, is relatively frequent in young diabetics. Shivelhood (1948) reported death with clinical evidence of myocardial infarction in a 12-year-old boy who had been a known diabetic since the age of two years Permission for autopsy was not obtained In recent years insulin has prolonged the life of diabetics, and more diabetics have been dying from coronary disease than from cerebral or peripheral vascular lesions (Bean, 1937).

Clawson and Bell (1949) analyzed the age and sex incidence of fatal coronary disease in autopsies of 49,593 nondiabetic and 1182 diabetic subjects. Fatal coronary disease was found to be about twice as frequent in diabetic as in nondiabetic men, and three times as frequent in diabetic as in nondiabetic women About 4 per cent of men and about 14 per cent of women, who died of coronary disease, had associated diabetes.

Ackerman and associates (1950) measured the degree of sclerosis in the coronary arteries in 600 women, including 25 with diabetes They determined that diabetics showed greater degrees (12 to 45 per cent) of coronary sclerosis than did nondiabetics, in each decade except the ninth.

Relationship of Cardiac Hypertrophy and Hypertension to Coronary Sclerosis. Approximately one-third (35 to 40 per cent) of persons with coronary occlusion have cardiac hypertrophy. Pre-existing hypertension favors the development of coronary sclerosis, sclerosis being more frequent and usually more severe among hypertensive than among nonhypertensive persons (Bell and Clawson, 1928, Master *et al*, 1939a; Ackerman *et al*, 1950). Levine and Brown (1929) stated that a previously existing hypertension is probably the most common single etiologic factor in the development of coronary thrombosis The tendency to coronary sclerosis among hypertensives is greater among men than among women (Davis and Klainer, 1940); this is in agreement with the common finding that hypertension in women runs a more benign and protracted course.

As previously mentioned, Faber and Lund (1949) on the basis of dry weights and of the content of cholesterol and calcium in 408 aortas, determined that hypertension is associated with an increase in the values of cholesterol and calcium which is greater than can be accounted for by age. Averbuck (1936) found that most patients with hypertension who died of heart failure (85 per cent in his series) suffered from severe coronary sclerosis while relatively few with hypertension who died from causes other than heart failure (only 10 per cent) showed marked coronary sclerosis Of 100 consecutive cases of acute coronary occlusion and myocardial infarction studied by Nay and Barnes (1945), 46 had normal blood pressures prior to the coronary occlusion and myocardial failure, 42 had hypertension previously, and in 12 the blood pressure previously was not definitely known.

Failure of hypertensive hearts, however, may occur without accompanying coronary disease and may be the result of myocardial weakness which is primarily related to factors concerned with the hypertension and the available blood supply to the myocardium In hypertensives there is no increase in the number of capillaries supplying the hypertrophied myocardial fibers, as compared to the number present in the heart of normal size (see page 553). The enlarged muscle fibers therefore have a relatively decreased blood supply. Should the coronary arteries become narrowed by atherosclerosis the nutrition of the muscle fibers is further compromised. The integrity of the myocardium depends upon sufficient nutrition per unit of muscular tissue. This means that for a given mass of muscular tissue there must be a sufficient number of blood capillaries,

with a sufficient flow of blood, and that the blood itself must be sufficiently oxygenated

Kaunitz (1947) has pointed out that in the adult heart in which the left coronary artery arises from the pulmonary trunk, the coronary lumen is dilated, the wall is thinner than normal, the media has a poorly developed muscular layer, and the intima has fibroelastic thickening. The lack of atherosclerosis in such a vessel, coupled with atherosclerosis in the right coronary, would seem to indicate that there is a relationship between intravascular pressure and the development of atherosclerosis, and would help to explain the frequent association of hypertension and severe coronary sclerosis.

Effect of Coronary Sclerosis on Development of Cardiac Hypertrophy. Coronary sclerosis, in itself, probably has relatively little influence on the production of cardiac hypertrophy and hypertension Aschoff (1933b) did not believe in the existence of arteriosclerotic hypertrophy of the heart, while Kaplan and associates (1938) indicated that it was not frequent. French and Dock (1944) were of the opinion that coronary disease causes no significant hypertrophy in the hearts of young men

Davis and Blumgart (1937), however, presented evidence that coronary sclerosis leads to cardiac hypertrophy presumably because impaired nutrition of the myocardial fibers induces stretching and hypertrophy of these fibers. Karsner (1949) states that hypertrophy occurs in infarcted hearts, independently of hypertension, and that it is probably caused by stretching of the remaining living muscle. From their study of the weight of hearts of soldiers who died of coronary disease, Yater and associates (1948c) also concluded that coronary artery disease alone may lead to hypertrophy of the left ventricle. It is believed that, when coronary occlusion leads to heart failure, the subsequent dilatation of the ventricle may be followed by some degree of myocardial hypertrophy but that hypertrophy in such cases is usually not of severe degree. Harrison and Wood (1949) maintain that cardiac hypertrophy is the rule in ischemic heart disease (coronary artery disease and myocardial infarction) and that it can be correlated with the duration of heart failure.

Boas and Boas (1949) state that they have had many patients with normal blood pressure under observation for years, and have observed progressive cardiac enlargement develop in them after myocardial infarction In every such patient one or more episodes of heart failure have followed the infarction.

Relation of Infection to Coronary Sclerosis. There is little evidence that acute or chronic infections favor the development of atherosclerosis in the coronary arteries.

In old syphilitic *infection* of the thoracic aorta one frequently sees superimposed atherosclerosis of a degree rarely encountered in the absence of syphilis. In syphilitic coronary arteritis, only the ostium and the first portion of the main stem of the coronary arteries are involved by the syphilis and there is usually little superimposed atherosclerosis; in the absence of syphilis, atherosclerosis of the main stem of the coronary arteries ordinarily develops at a short distance beyond the ostia.

On the basis of a careful study, Karsner and Bayless (1934) concluded that preexisting *rheumatic disease* of the coronaries predisposed the vessels to arteriosclerosis, Gross and Oppenheimer (1936), however, from an analysis of their own material, were led to believe that these two lesions were independent and unrelated. Myocardial scars of small size may possibly be the result of old rheumatic disease, but they usually represent the

effect of atherosclerotic occlusion of small branches of the coronary arteries.

Many writers believe that rheumatic disease has an allergic basis, (see Chapter VIII). Rich and Gregory (1947) sensitized 45 rabbits to horse serum and in 18 produced "sclerotic" lesions of the branches of the coronary arteries which were comparable to those caused by rheumatic fever. They thought these lesions to be similar to those found in disseminated lupus erythematosus and in a large number of other diseases. The inference is that allergy may possibly be a factor in man in the production of coronary sclerosis.

Saphir (1936) reported the occurrence of severe arteriosclerosis in the coronary arteries which were also the seat of *thromboangiitis obliterans* in a 35-year-old man He believes that the latter may have been a factor in the production of arteriosclerosis. Saphir and Gore (1950) examined sections from multiple blocks of the myocardium and major coronary arteries from 13 male soldiers, ranging in age from 18 to 29 years, who died suddenly and unexpectedly of severe coronary heart disease. They found evidence for an inflammatory basis of coronary arteriosclerosis in 10 of these patients in the large coronary arteries or the small intramyocardial arteries.

Syphilitic Disease of Coronary Arteries. In approximately one-third of patients with syphilitic mesaortitis, the orifice of one or both coronary arteries is reduced in circumference (Saphir and Scott, 1930, Bruenn, 1934) Bruenn found that the circumference of the orifice of the normal coronary artery was 8 to 10 mm. The ostium of a coronary is more likely to be involved if it is anomalously located above the sinus of Valsalva (Von Glahn, 1923; Martland, 1930). In 1000 consecutive autopsies, Von Glahn (1936) found that in 80 (8 per cent) one or both coronary arteries arose above the upper level of their respective sinuses of Valsalva. In a series of 133 cases of syphilitic aortitis (Turner, 1950), the orifice of either one or both coronary arteries was involved in 19 hearts. The orifice of the right coronary artery was narrowed in 15 instances and occluded in 2; that of the left coronary was narrowed in 11 and the orifices of both vessels were narrowed in 7. In every instance but one, the involved coronary artery arose either at the upper level of the respective sinus of Valsalva or above this line. Inasmuch as the syphilitic lesion usually stops at the upper level of the sinus, origin of a coronary artery above this level is regarded as an important factor in its involvement by syphilis. The relative frequency of origin above the sinus of Valsalva in the two arteries should be given, if possible In Bruenn's series of 39 cases of syphilitic coronary arteritis, the orifice of the right coronary artery was totally occluded in 8 instances, that of the left coronary in one. Syphilitic coronary arteritis is not limited to the portion of the artery included in the wall of the aorta but may extend 10 to 12 mm beyond the orifice to produce stenosis or occlusion of the lumen (Moritz, 1931). It rarely extends more than 1 cm. beyond the orifice Such narrowing of the coronary arteries may gradually progress to the point of complete occlusion and yet the heart may show no evidence of myocarditis, fibrosis or infarction The ostia of both coronary arteries were completely occluded in two instances reported by Leary and Wearn (1930), the myocardium, however, was of normal appearance, anastomotic channels enabling the heart to perform its ordinary functions With extra exertion or emotion, however, such subjects are likely to suffer attacks of angina pectoris; they are particularly exposed to the danger of sudden death Occasionally syphilitic structural changes contribute to myocardial infarction (Bean, 1937) but only in rare cases does syphilitic narrowing

of the coronary ostia actually lead to this condition. It occurred in only three of 39 hearts with syphilitic coronary stenosis studied by Bruenn, and in three of 40 studied by Burch and Winsor (1942). Kobernick (1947) reported myocardial infarction as a result of gumma of the right coronary artery with secondary thrombosis of the artery. The average age of patients with syphilitic stenosis of the coronary ostia is about 45 years The condition is commoner among Negroes than white persons, among men than among women.

Martland (1930) reported aneurysm of the artery with rupture into the pericardial sac and death.

Relation of Thyroid Disease to Coronary Sclerosis. In hyperthyroidism there is an increased amount of work thrown upon the heart and usually a mild to moderate degree of cardiac dilatation and hypertrophy.

In experimental animals rendered hyperthyroid by the injection of thyroxin and in persons with hyperthyroidism, Rake and McEachern (1932) found no specific myocardial lesions. Weller and associates (1932) in a study of 35 hearts from subjects with exophthalmic goiter found a relatively high incidence of (a) myocardial fibrosis (80 per cent) which was not related to vascular obliteration, (b) endocardial sclerosis (89 per cent) and (c) cellular infiltrations (31 per cent). In a control series of patients of the same age and sex, without thyroid disease and with no evidence of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis, these changes were less frequent (myocardial fibrosis was found in 51 per cent, endocardial sclerosis in 51 per cent and cellular infiltrations in 17 per cent).

Myxedema is commonly associated with increased hypercholesterolemia, coronary sclerosis and an enlarged rounded heart. Caution must be exercised in the therapeutic use of thyroid extract in myxedema, particularly if the patient develops angina during administration of the drug. Smyth (1938) summarized the findings in five cases of myxedema reported in the literature in which autopsy revealed myocardial infarcts. He added a case of his own in which a patient with myxedema and angina pectoris developed myocardial infarction while under treatment with thyroid substance.

Myocardial Infarction and Sudden Death Following Administration of Drugs. Mills and associates (1949) reported four instances of severe myocardial ischemia, with three deaths, following injection of Pitressin as a diagnostic aid in cholecystography. The injection of the drug, a powerful coronary vasoconstrictor, was believed to have been responsible. McNerney and Leedham (1950) reported the occurrence of clinical acute myocardial infarction following intravenous injection of 0.5 mg. (1 ml.) ergotamine tartrate (Gynergen).

In a 52-year-old woman who died apparently of acute cardiac failure, following the subcutaneous injection of four ampules (one daily for four successive days) of 0.5 ml. 1:2000 (0 25 mg.) ergotamine tartrate (Gynergen), the small coronary arteries (Figure VII-8) showed apparent thickening of the walls and marked reduction of the lumen (Gould *et al.*, 1936) The main coronary arteries also appeared to be narrowed but no myocardial changes were observed.

Coronary Occlusion, Coronary Insufficiency

Occlusion Following Hemorrhage in Atherosclerotic Coronary Arteries. Paterson (1936) and Wartman (1938) have described occlusion following bleeding in the intimal lesions of atherosclerotic coronary arteries. According to Paterson, intimal capillaries often arise directly from the lumen (rather than from the vasa vasorum) of the coronary arteries in association with



Figure VII-8. Constriction of small coronary artery in woman who developed gangrene of the lower extremities and died in acute heart failure four days after receiving ergotamine tartrate intramuscularly. (WCGH, 36 A 1)



Figure VII-9 Hemorrhage in sclerotic intima of coronary artery with rupture into lumen of vessel X 100. (WCGH, 40 A 91.)



Figure VII-10. Another segment of same section of coronary artery as that shown in Figure VII-8, showing intramural hemorrhage and thrombosis. X 100.

atherosclerosis He believes that, as a result of (a) softening, by the atheroma, of the tissues surrounding and supporting the capillary wall, and (b) high intracapillary blood pressure, there is rupture of the intimal capillaries and hemorrhage in the intima. Damage to the endothelium by extravasation of blood then leads to coronary thrombosis. Paterson states that the intimal capillaries, arising directly from the lumen, are constantly exposed to the relatively high blood pressure within the coronary lumen; they are thus subject to sudden increases in coronary blood pressure. For this reason excessive exercise and emotional stress are intimately concerned with intimal capillary rupture and, therefore, may be factors in the production of coronary thrombosis. He (1938) found such hemorrhagic foci at the site of thrombotic occlusion in 31 of 36 consecutive cases. Paterson claims that high blood pressure within the coronary lumen is a factor in the production of internal hemorrhage in the vessel wall and submits evidence to show that such hemorrhages are more frequent in hypertensive than in nonhypertensive subjects.

Wartman (1938) encountered hemorrhage, usually massive, in the intimal lesions, which caused stenosis of the lumen of the affected artery. The occlusion of the

coronary artery was caused solely by the intramural hematoma in 15 per cent of 41 instances, in 34 per cent of the others, intramural hemorrhage and thrombus were associated (Figures VII-9 and VII-10). It seemed probable that the thrombus had been formed as a result of hemorrhage following rupture of capillaries The intima in the region of the hemorrhage was always richly vascularized by capillaries. In six of seven cases reported by Wartman, the intimal hematoma was covered by intact endothelium and no thrombus was found in the lumen. In a subsequent report, Wartman (1949) estimates that in about 60 per cent of cases of coronary occlusion, hemorrhage into the intima is the precipitating factor. In approximately 10 per cent the occlusion is due to an expanding hematoma; in about 20 per cent the hemorrhage is not large enough to obstruct the lumen completely, but a thrombus may be associated, and in more than 30 per cent occlusion is caused by rupture of the hematoma through the intima with subsequent thrombosis. Wartman (1950) has also described similar thrombosis following intramural bleeding in arteriosclerotic iliac and femoral arteries.

French and Dock (1944), however, found hemorrhages in the atherosclerotic plaques of the coronaries of only five of 80 soldiers with fatal coronary sclerosis. Yater and associates (1948c) encountered hemorrhage in atherosclerotic plaques in 12 per cent of subjects who died suddenly from coronary artery disease.

In this connection, it may be pointed out that the ingrowth of blood capillaries about atherosclerotic plaques in the coronary arteries usually comes from the vasa vasorum and only occasionally from the intima (Wolkoff, 1929; Ehrich *et al.*, 1931; Leary, 1938). Winternitz and associates (1937, 1938) have advanced the idea that hemorrhage from capillaries in the walls of the aorta or coronary arteries is an important factor in the production of atherosclerosis. Just how frequently this sequence of events occurs remains to be determined.

Kowalczykowa (1934) reported the occurrence, in a man aged 80, of spontaneous rupture of an arteriosclerotic branch of the left circumflex coronary artery; this led to a subepicardial hematoma and to secondary and fatal hemorrhage into the pericardial sac.

Fatal Coronary Occlusion or Insufficiency Without Infarction. Blumgart and associates (1941a) explained the occurrence of complete coronary occlusion or severe narrowing of one or more coronary arteries without evidence of myocardial infarction, by the slow progress of the obstructing lesion which allows sufficient time for the formation of an adequate collateral coronary circulation. In 47 of their patients who had suffered primarily from angina pectoris without evidence of valvular disease or arterial hypertension, they found old complete occlusion of at least one major coronary artery at autopsy. Kaisner (1949) states that he has not observed infarction to result from gradual occlusion of the coronary arteries by arteriosclerosis.

York and Bell (1946) believed that, in a significant number of cases of coronary artery disease, myocardial ischemia rather than true myocardial infarction, may result in an abnormal cardiac rhythm, probably ventricular fibrillation, and be responsible for death. Holyoke (1945), by injection of the coronary arteries by Schlesinger's method, found old occlusions in 11 hearts, in three of which no old infarcts were present; he also encountered five hearts with recent occlusions, two of which showed no recent infarction. Ravin and Geever (1946) demonstrated coronary occlusion in 18 injected hearts, in five of these 18, infarction was absent.

In approximately three-fourths of cases of sudden death from coronary insufficiency, no gross myocardial infarction was

found by Yater *et al.* (1948c). In most of these cases, the coronary arteries showed sclerotic occlusion without thrombosis; a lesser number, sclerotic occlusion and thrombosis, and a small percentage, neither sclerotic occlusion nor thrombosis. When sudden death occurs from a rapidly forming thrombus at the site of an atherosclerotic plaque, *before myocardial necrosis* appears, the heart usually shows evidence of previous damage (Monckeberg, 1924) The development of thrombosis of an atherosclerotic vessel further reduces the capacity of the coronary artery to nourish the myocardium adequately and thus increases the chance of death from acute insufficiency

Hypoxemic Necrosis Following Coronary Insufficiency. Buchner (1939) has described foci of "hypoxemic necrosis" of heart muscle resulting from an acute or chronic deficiency of oxygen in its blood supply (coronary insufficiency) The causes include atherosclerotic stenosis of coronary arteries, syphilitic narrowing of the ostia of the coronary arteries, circulatory shock, aortic insufficiency, severe anemias, subacute carbon monoxide poisoning, breathing air with reduced oxygen content especially at high altitudes (15,000 feet and higher), massive pulmonary embolism, and chronic ventricular hypertrophy with decompensation According to Buchner, the necrotic foci of muscle are of microscopic size, and at first show loss of striations of the fibers, coagulation of the sarcoplasm into a homogeneous mass, and shrinking of the nuclei. The nuclei then disappear and in the course of about 24 hours, the necrotic fibers become infiltrated with polymorphonuclear leukocytes. The fragmented necrotic material is liquefied by ferments (from the serum) and resorbed, the local connective tissue cells actively proliferate and, in the course of days, the necrotic focus is replaced by fibrous tissue which forms a small scar At times the coronary insufficiency, which is responsible for the necrotic foci, is attended by angina pectoris and an electrocardiogram may show depression of the S-T segment below the isoelectric line. The sites of predilection of these necrotic areas are the inner layers of the left ventricle and the papillary muscles and trabeculae of this chamber. When coronary insufficiency involves chiefly the right ventricle, as in massive pulmonary embolism, hypoxemic necrotic foci may be encountered in the right ventricle.

Beck (1938) reviewed the clinical effects and pathologic changes caused by carbon monoxide poisoning. He emphasizes that it is not generally recognized that, in addition to acute asphyxiation, the gas may cause disability or death from the remote effect of acute poisoning and from the chronic effect of slow but persistent poisoning. These effects result chiefly from anoxemic changes induced in the myocardium, with hemorrhage and necrosis, or from coronary thrombosis.

Dack and associates (1949) have presented electrocardiographic and anatomic evidence of acute coronary insufficiency caused by pulmonary embolism. They found that the left ventricle is affected adversely and often to a greater extent than the right ventricle. In their series of 41 fatal cases of pulmonary embolism they found the electrocardiographic pattern of acute coronary insufficiency (RS-T depression and T wave inversion in one or more leads) more often than the pattern of acute cor pulmonale (deep S_1 and Q_3, depressed RS-T in lead 1, elevated RS-T in lead 3, and T_3 inversion). Ten subjects (24 per cent) had myocardial necrosis or infarction resulting from the acute coronary insufficiency, and none of these had acute occlusion of a coronary artery. In three of the 10 subjects, gross changes were apparent The commonest sites of necrosis were the subendocardial layer of the left ven-

tricle and the papillary muscles. The right ventricle was involved in only one case. They believe that the principal exciting factors in the diminished coronary blood flow and myocardial anoxia are systemic shock, right ventricular dilatation, anoxemia and possibly reflex coronary vasoconstriction.

Master and associates (1950) demonstrated subendocardial lesions in patients suffering from evidences of acute coronary insufficiency following acute hemorrhage, particularly of the gastrointestinal tract. As in the lesions described by Buchner (1939), the subendocardial layers of the posterior wall, septum and papillary muscles of the left ventricle contained focal or grossly recognizable confluent areas of myocardial necrosis The necrotic muscle had a uniform appearance with loss of striations, changes in staining ability and loss of nuclei, together with scattered hemorrhages and reactive cellular infiltrations. The lesions were more severe in patients in whom the myocardial ischemia was protracted and in those with such previous cardiac disease as severe coronary sclerosis, cardiac hypertrophy or aortic valvular disease.

Highman and Altland (1949) exposed rats to an altitude of 25,000 feet for four hours daily with a resulting striking reduction in their life span, none of the animals living more than one-half their normal life span. Nearly all the animals had severe vascular engorgement Most of them had hypertrophy of the heart and thickening of the cardiac valves. Many had vegetations (usually sterile) of the valves, particularly of the mitral valve, *subendocardial fibrosis* of the left ventricle and fatty and other degenerative changes of the myocardium. One rat had thrombotic coronary occlusions and extensive myocardial infarction These changes apparently are the result of repeated episodes of hypoxemia and coronary insufficiency, and of secondary polycythemia.

Aging of Myocardium. Dock (1945) has applied the term *presbycardia* to indicate myocardial senescence or that age has impaired the function of the heart even though there is no significant structural change. He believes that, in older persons without coronary arteriosclerosis, this condition is often the basis for heart failure. Likewise, Harrison and Resnick (1950) state that clinically the term *arteriosclerotic heart disease* should be restricted to patients having angina pectoris or evidence of myocardial infarction and should not be applied to elderly persons suffering from heart disease and congestive failure without obvious cause. They believe that the aging myocardium undergoes involutionary changes for which there is no recognized histologic basis and no known clinical defect; that these involutionary changes may lead to heart failure; and that this condition should be designated *senile heart disease*.

MYOCARDIAL INFARCTION

Etiologic Considerations

Morbidity and Mortality. See discussion on Morbidity and Mortality from Coronary Disease, page 567.

Myocardial Infarction in Infancy. Ravich and Rosenblatt (1947) found no reported cases of myocardial infarction in the newborn and only four in infancy. They studied myocardial infarction in two newborn infants, one aged 10½ hours and one two days. In the first case there were thrombi in the coronary arteries and veins and an infarct in the dorsal wall of the left ventricle. The thrombosis was related to trauma incident to birth. In the

second case, branches of the coronary arteries showed medial sclerosis and thrombosis. Ellis (1935) reported in a nine-month-old hydrocephalic infant, aneurysmal formations at and above the apex of the left ventricle occurring within an area of infarction. Jokl and Greenstein (1944) described fatal coronary sclerosis in a boy of 10 years who died five minutes after a boxing match. The descending branch of the left coronary was obstructed by a thrombus one inch long, beginning one-half inch from the orifice. Above and below the occlusion there were atheromatous changes in the intima Histologically, the vessel was almost completely occluded. The intima was considerably thickened and hyalinized There were several plaques of calcium between the intima and media and the surrounding tissues were infiltrated with erythrocytes The internal elastic layer was disrupted and completely absent in parts.

Severe coronary atherosclerosis with occlusion and myocardial infarction may also be seen in early childhhod in familial hypercholesterolemia and xanthomatosis (see pages 563 to 570)

Coronary Occlusion and Myocardial Infarction under 40 Years of Age. Underdahl and Smith (1947) found reports of only 27 women with clinical coronary artery disease among 95,000 women under 40 who were seen at the Mayo Clinic between 1935 and 1945 Seven had definite myocardial infarction and two questionable infarction They believe that coronary disease in women under the age of 40 is rare except in association with obesity, hypertension or hyperlipemia. Evans and Graybiel (1948) reported fatal coronary thrombosis in a woman of 19 with hypertension. They believe that their patient was the youngest woman on record with fatal thrombosis. At autopsy they found occlusion of the right coronary, arteriosclerotic narrowing of the lumen of the left coronary, and areas of myocardial scarring. Moritz and Zamcheck (1946) reviewed the autopsy protocols of 1000 soldiers under the age of 40 who died suddenly and unexpectedly. More than 200 deaths were attributed to coronary disease; in all of the subjects severe atherosclerosis was found in one or both coronaries. Yater and associates (1948a) reviewed the literature on coronary artery disease in persons under 40. The total number of persons reported to be under 20 years of age was 14 (9 males, 3 females, 2 sex not stated); between 20 and 29 years, 128 (109 males, 3 females, 16 sex not stated); under 40 years, 744 (597 males, 29 females, 118 sex not stated). These totals include the report of Meesen (1944) of 326 German soldiers, of whom 78 were between 20 and 29 years of age. Yater and associates studied the clinical findings in 866 cases of coronary artery disease in soldiers between the ages of 18 and 39 years, inclusive, and the pathologic findings of 450 of these subjects who came to autopsy. Death from this disease was more than thirty times as frequent in men aged 35 to 39 years, inclusive, as in men aged 20 to 24 years, inclusive.

Age at Onset of Angina Pectoris and Myocardial Infarction. Riseman and Brown (1937) in 100 patients with clinically proved angina pectoris in whom symptoms were induced by a standard exercise, determined the age of onset as follows. 5 per cent in the thirties, 30 per cent in the forties, 49 per cent in the fifties and 16 per cent in the sixties The average age at onset of infarction in 222 patients studied by Bean (1937) was 61 years (males 60.1 years, females 61.7 years), approximately 10 per cent of the subjects being in the forties, 25 per cent in the fifties, and 35 per cent in the sixties. Chambers (1946) followed 100 consecutive patients after their initial attack of acute myocardial infarction. The ratio of men to women was 3 to 1. The women in the series

were older and their mortality rate was higher than that of the men. This is true in most studies of a similar nature.

Incidence of Myocardial Infarction at Autopsy. In 5200 autopsies, Rintelen (1932) of the Basle Pathological Institute found that fresh myocardial infarction was regarded as the primary cause of death in 51 instances (1 per cent). Barnes and Ball (1932) of the Mayo Clinic, in a series of 1000 consecutive autopsies, found 49 hearts with old or recent infarcts (4.9 per cent) Forty of the subjects were men, 9 were women. In 18 the infarct was the cause of death, in 19 a contributory cause, in 7 a possible contributory factor, and in 5 it was not an appreciable factor in causing death. McCain and associates (1950) of Western Reserve University reviewed 3559 autopsies which were performed during the ten-year period from 1936 to 1945 inclusive. Myocardial infarcts were found in 281 subjects (7.8 per cent), of whom 198 were male and 83 female. This gave an incidence of 8 7 per 100 autopsies in males and 6 5 per 100 autopsies in females, or a corrected ratio of men to women with myocardial infarcts of 1.3:1. The average age at death for men was 60.9 years, for women 62.9 years; for Negroes 56.1 years and for white subjects 62 2 years. Among 149 patients it was possible to determine the date of occurrence of the infarction and in 95 of these, death occurred within one month after onset.

Incidence of Sudden Death from Coronary Disease. Sudden death may be defined as unexpected death occurring within 24 hours of the onset of symptoms.

Hamman (1934) analyzed reports of series of sudden deaths by several authors and calculated that 91 per cent of 700 such deaths from natural causes were due to diseases of the cardiovascular system and 40 per cent of all sudden deaths from natural causes were due to disease of the coronary arteries. The most important natural causes of sudden death and their relative incidence were as follows:

Cause of Death	*Per Cent*
Disease of the coronary arteries, including syphilitic occlusion of ostia	40
Aneurysm of aorta	12
Valvular heart disease	12
Myocardial disease	8
Cerebral hemorrhage	8
Pulmonary embolism	5
Pulmonary hemorrhage	5
All other causes	10

In a series of 500 cases of sudden cardiac death subjected to legal autopsy in Copenhagen, Munck (1946) found that 79 per cent were associated with coronary sclerosis, 11 per cent with syphilitic aortitis and 4 per cent with valvular disease, mainly aortic stenosis. Twenty per cent of those with coronary disease revealed no occlusion or myocardial infarction, 36 per cent had thrombosis, and 19 per cent fresh infarction In a series of 2030 cases of sudden and unexpected natural death in New York City, Rabson and Helpern (1948) determined that in 45 per cent of cases death was attributable to diseases of the heart and aorta, and in 30 per cent to coronary sclerosis. In three-fourths of the deaths from coronary sclerosis, coronary occlusion was not associated with thrombosis, and in the remaining fourth, the thrombus was not always fresh.

In a series reported by Moritz and Zamcheck (1946) of 115 cases of sudden death among American soldiers from coronary arteriosclerosis, coronary thrombosis was found in 31, sclerosis without thrombosis in 23 and severe sclerosis without thrombosis or obliteration in 61. In 22 hearts, infarcts were present; 15 of these were recent and 7 were old; 27 other hearts had myocardial fibrosis but myocardial infarction was not recognized. (See also Cardiac Le-

sions in Sudden Death from Coronary Insufficiency, page 592.)

It is thus seen that heart disease is the commonest cause of sudden death from natural causes, that the commonest type of heart disease at fault is disease (sclerosis) of the coronary arteries; and that in most instances of sudden fatal coronary disease, neither arterial thrombosis nor fresh myocardial infarction is present

Sex Incidence in Myocardial Infarction. Master and associates (1939b), in a study of 500 patients with myocardial infarction from coronary occlusion, found a ratio of men to women of 3 4 to 1 Connor and Holt (1930) encountered coronary thrombosis among men in 85 per cent of their cases, Baker and Willius (1938) found that men and women were affected in a ratio of 7 to 1 and Chambers (1946) found a ratio of 3 to 1.

The preponderance of coronary occlusion among men is also apparent at autopsy Nathanson (1932) stated that coronary disease among nondiabetics is three times as common in men as in women Among 496 subjects with severe coronary sclerosis whose autopsy findings were analyzed by Bruenn and associates (1936), the ratio of men to women was greater than 3 to 1

Yater and associates (1948a) collected reports from the literature of patients under 40 with coronary artery disease. Excluding the figures of Meesen for soldiers in the German Army, these reports cover a total of 271 males and 29 females under 40, a ratio of about 9 males to 1 female, 31 males and 3 females between 20 and 29 years, and 9 males and 3 females between 10 and 20.

Race Incidence of Coronary Thrombosis and Myocardial Infarction. Peery and Langsam (1940) reported that coronary thrombosis in the Negro, with or without hypertension, was relatively rare. Among persons over 30 years of age who died of



Figure VII-11. Anomalous origin of right coronary artery with narrowing of ostium of the artery by extension of syphilitic aortitis (WCGH, 47 A 81)

cardiovascular disease, coronary thrombosis was responsible for death in 3 0 per cent of Negroes and in 14.6 per cent of white subjects Fitzgerald and Yater (1946) determined from the autopsy records of a Washington (D.C) hospital that Negroes had a tendency to die of myocardial infarction about a decade earlier in life than did white persons Yater and associates (1948) studied the incidence of fatal coronary artery disease in the United States Army among men between the ages of 18 and 39 years, inclusive. In their series, the incidence among Negroes was approximately two-thirds that among Caucasians. (See also page 562)

Occlusion of Anomalous Coronary Arteries. The orifice of the right coronary artery is frequently (8 per cent of persons) located in the wall of the aorta above its normal position in the cusp (Von Glahn, 1936) and accordingly is particularly disposed to involvement by syphilitic aortitis (Figure VII-11). In this abnormal situa-

tion, it is also more likely to be occluded by an atherosclerotic plaque.

A single coronary artery may take over the function of the absent vessel, without damage to the myocardium, and appear at autopsy as an incidental finding (Krumbhaar and Ehrich, 1938).

Roberts and Loube (1947) reviewed 31 cases of congenital single coronary artery (single right artery, 17, single left artery, 11, identity of artery undetermined, 3). The average age was 39 years, 4 of the patients were less than 10 years old, 14 over 40 years of age. Absence of the left coronary artery (the single artery being the right coronary artery) was associated in 4 patients with myocardial infarction, and in 3 patients with myocardial fibrosis or ischemia. This indicates that the right coronary artery alone is less able to maintain an adequate blood supply to the heart than is the left artery alone.

Dutra (1950) reported, in a five-month-old male infant, origin of the left coronary artery from the first portion of the right branch of the pulmonary trunk. The branches of the left coronary artery showed thickening of the intima while the left ventricle showed subendocardial fibrosis and two recent infarcts together with *fibrosis and calcification of the myocardium.*

Either coronary artery or both coronary arteries may arise from the pulmonary trunk. Origin of the right coronary from the pulmonary is rare, having been reported twice (Monckeberg, Schley, consult Kaunitz, 1947), both in adults. In these cases both coronaries were dilated, the right one being thin-walled and resembling a vein. Kaunitz reviewed 27 cases, 20 in infants aged 2½ to 13 months and 7 in adults aged 17 to 64 years, in which the left coronary took its origin from the pulmonary trunk. In such cases there is chronic anoxia of the portions of the heart supplied by the left coronary, with shrinkage, fibrosis, and calcification of the left anterior papillary muscle. If the collateral circulation is inadequate between the coronary arteries or between the left coronary and the left ventricular cavity, the left ventricle may show dilatation and hypertrophy and even aneurysmal bulging, fibroelastic thickening of the endocardium, focal areas of calcification and dilated sinuses in the myocardium, while the left coronary artery is wider and thinner than normal, its media showing a poorly developed muscular layer and its intima having fibroelastic thickening.

Only two cases have been reported in which both coronaries arose from the pulmonary trunk, in each of these, life was maintained for only 10 hours (Limbourg, 1937; Grayzel and Tennant, 1934). The cardiac hypertrophy that occurs as a result of anoxia when the left coronary arises from the pulmonary trunk is regarded as strong evidence that chronic coronary insufficiency can cause cardiac hypertrophy

Coronary Occlusion in Dextrocardia. Clinical coronary occlusion has been reported (Crawford and Warren, 1938) in a patient with situs inversus and congenital dextrocardia. The pain was localized in *the right side of the chest and there was* numbness in the right arm.

Occurrence of Pain in Coronary Artery Disease. Cardiac pain is generally an indication of relative myocardial ischemia resulting from impairment of the coronary circulation. It occurs in approximately 20 per cent of subjects with atherosclerotic narrowing of the coronaries and in approximately 40 per cent of those with atherosclerotic occlusion or thrombosis (Bruenn *et al.*, 1936). Angina pectoris in patients without valvular disease or hypertension has been related to old complete occlusion of at least one of the three main coronary arteries (right coronary, left anterior descending branch or left circumflex

branch); complete occlusion of one or more of these coronary arteries, however, may exist without giving rise to any symptoms and may be unassociated with any evidence of myocardial damage (Blumgart *et al.*, 1941a)

A history of cardiac pain may be obtained in approximately 95 per cent of patients with fresh or recent myocardial infarction (Yater *et al.*, 1948a), but only in a majority of patients with old infarcts (Kennedy, 1937; Gorham and Martin, 1938). Nearly all of the patients with fresh myocardial infarction who do not suffer cardiac pain give a history of dyspnea or weakness

Landman and associates (1949) undertook a study of asymptomatic myocardial infarction In checking the clinical history of 255 patients in whom myocardial infarction was encountered at autopsy, it was determined that pain, shock, dyspnea and congestive failure had been absent during life in 28 (11 per cent) An analysis of their data, however, shows that only 9 subjects (3 5 per cent) had fresh infarcts without associated cardiac symptoms; this latter incidence may be accepted as fairly representative

Hirsch and Orme (1947) demonstrated sensory nerve fibers which terminate in the wall of the coronary arteries. They postulate that the stimuli that produce pain in coronary disease arise in arterial and periarterial tissues rather than in anoxemic myocardium as is generally held. In painless myocardial infarction, the absence of pain of anginal type is attributed to localized destruction of afferent pain fibers in periarterial plexuses of coronary arteries supplying the ischemic areas of myocardium (Harrison and Resnick, 1950)

Factors in Causation of Myocardial Infarction. Myocardial infarction is the result of sustained relatively severe myocardial ischemia In most cases the ischemia is caused by coronary occlusion, this may be sudden, as in embolism; relatively sudden, as in thrombosis, especially when thrombosis results from hemorrhage into the wall or into the lumen of the vessel; or gradual, as in coronary atherosclerosis without thrombosis. Gross (1921) lists the following determining factors in the production of myocardial infarcts: (a) size of obliterated vessel; (b) location of obliterated vessel, (c) duration and rapidity of obliteration, (d) condition of general circulation and of the heart musculature; and (e) age of the individual. He regarded the age of the individual affected as of prime importance, since the older the person, the greater and freer are the anastomoses and the better will he be able to withstand the effects of sudden obliteration of a nutrient vessel. In appraising the condition of the heart musculature, one must consider the presence of concomitant disease in other branches of the coronary arteries and the presence and degree of cardiac hypertrophy Miller (1939) pointed out that possible contributory factors in myocardial infarction include those which change the blood and those which lessen coronary flow. He reported seven cases of polycythemia vera which came to autopsy; of these, three had myocardial changes with coronary occlusions, two myocardial changes but no coronary occlusion, and two neither myocardial changes nor coronary occlusion.

In polycythemia vera, the viscosity of the blood is increased, the blood stream is slowed and the tendency to arterial thrombosis, including coronary thrombosis, is increased, particularly if arteriosclerosis is associated (Boas and Boas, 1949). In 33 of 98 patients (34 per cent) with polycythemia vera seen at the Mayo Clinic (Norman and Allen, 1937) vascular complications were present; five of these 33 patients had disease of the coronary arteries. Diminution of coronary flow follows (1) lowering of diastolic blood pressure, (2)—

decrease in systolic output, and (3) constriction of coronary arteries (Luten, 1931).

Among *precipitating factors* in acute coronary occlusion, Bean (1937) includes exposure to very low temperatures, infections, spontaneous and insulin hypoglycemia, indirect trauma, operative trauma, anesthesia, hemorrhage, and shock. Occupation and activity did not seem to be important factors Blumgart and associates (1941b) stress the danger of shock in elderly patients, particularly in those with evidence of coronary arteriosclerosis. In such patients shock may induce not only single, but often multiple, fresh infarction Boas (1942) believes that, in the presence of diseased coronary arteries, the commonest external factors precipitating myocardial infarction are effort, emotion, exposure to cold, and over-eating Among other factors which may induce angina pectoris or myocardial infarction, he includes serum sickness induced by injection of tetanus antitoxin (see McManus and Lawlor, 1950), infectious disease, operation and hemorrhage, insulin shock and hypoglycemia, exposure to high altitudes, and excessive heat or humidity.

Borst and Holleman (1948) caution against the danger of acute coronary insufficiency or myocardial infarction from the rapid intravenous administration of sodium chloride to patients with latent coronary insufficiency or congestive heart failure

Bean (1937) found that approximately one-third of patients with myocardial infarction had a previous history of angina pectoris. In reviewing the work of other authors, he found preceding hypertension in 34 per cent of a total of 751 cases of myocardial infarction. Among 270 of the patients in his own series, one-half had a systolic pressure over 160 mm. mercury and a diastolic pressure over 100 before the infarction. It may be conservatively stated that approximately one-half of all patients with myocardial infarcts have or have had hypertension and cardiac hypertrophy.

Paterson (1939, 1940) stated that rupture of intimal capillaries, which may lead to coronary thrombosis, may in part be induced by intraluminal pressure, and therefore recommended that all patients with coronary disease be advised to avoid excessive exertion or emotion or any other activity which may raise their intracapillary pressure.

Blumgart and associates (1941) produced massive infarction in dogs by obstructing the blood supply to the heart for 40 minutes or longer. They believe that in man myocardial infarction may occur, first, after sudden occlusion of a vessel which was previously adequate, if sufficient collateral anastomoses have not yet developed, and second, without occlusion of a vessel, if the myocardial anoxemia is sufficiently prolonged. In some patients whose myocardium suffers temporary ischemia because of occlusion or narrowing of the coronaries, infarction is favored by increased demands upon the heart, as by continuation of physical effort.

Yater and associates (1948a) in their analysis of 866 clinical cases of acute coronary artery disease in American soldiers under the age of 40, including 450 who came to autopsy, found that the number of attacks occurring at the time of strenuous activity was more than twice the proportion of time spent in such activity, while the number of attacks occurring during sleep was about one-third the proportion of time spent in sleep. They concluded that in certain cases, a thrombus or infarct may have been forming silently for some time and the type of activity at the onset of symptoms was purely coincidental; while in other cases activity, especially if strenuous, may have caused the additional

demand for coronary blood flow that precipitated the fatal attack.

Among these 450 soldiers, death occurred within 24 hours in 83 per cent; infarction was absent in 75 per cent In general, the longer a man lived following the onset of the attack of coronary disease the more likely was infarction to be present at autopsy. Patients with a previous cardiac history tended to have infarcts more often than those without such a history; those with a cardiac history also tended to have myocardial scars more often.

Myocardial Infarction and Rate of Development of Coronary Occlusion. Clinicopathologic and experimental studies have shown that if the occlusion of a main branch is sudden, the area of infarction is large but if the occlusion develops slowly, there may be little or no necrosis When the obstruction is gradual, anastomotic vessels develop and the heart is better able to withstand the effects of the occlusion. Most cases of sudden closure of the anterior descending vessel result from embolism of a thrombus or vegetation in the left ventricle or on the root of the aorta, in a previously damaged heart. Monckeberg (1924) states that sudden closures of the right coronary artery in man may be survived; and that sudden closures of the anterior descending branch of the left coronary may be survived only if there are many pre-existing anastomoses, the other coronary arteries are relatively free of disease, and the cardiac reserve is good Myocardial infarction is associated with occlusion of at least two branches of the coronary arteries supplying the infarcted area (Saphir *et al*, 1935)

Schlesinger (1938) found an infarct which resulted from rapid occlusion of a major branch, although all other branches were normal (Case 19), in four of six hearts examined he found two occlusions Smith and Hinshaw (1937) reported severe progressive angina pectoris in a patient aged 31, following recovery from myocardial infarction. Chambers (1946) observed 100 patients in their initial attack of acute myocardial infarction. Thirty-four died within 30 days, eight others within one year. Of the remaining 58, nine had nonfatal recurrent infarctions within the year Of the other 49 about one-half had angina pectoris, eight had some symptom of cardiac insufficiency and 11 had no symptoms. Yater and associates (1948a) found that 57 of their 450 subjects who came to autopsy had had anginoid attacks three or more weeks before death Among 440 who survived an attack of coronary insufficiency, 77 developed angina of effort and an additional 64 developed other attacks of coronary insufficiency In 10 per cent of survivors, there was exacerbation of pain on deep inspiration

Visualization of Coronary Arteries During Life. According to Snellen and Nauta (1937), calcification of the coronary arteries may be recognized with the fluoroscope by dancing shadows seen in locations corresponding to those of the arteries. In five patients, the x-ray diagnosis was confirmed at necropsy Radner (1945) attempted by roentgenograms to demonstrate the outlines of coronary arteries in five human subjects by injecting Thorotrast into the ascending aorta. Two patients developed transient complications. A suggestive result was obtained in one patient Jonsson (1948) obtained filling of one or both coronaries in five subjects by injecting contrast medium through a catheter the tip of which reached the aortic valve. While admitting that the technic is still imperfect, he claims that the method is harmless. Gordon and associates (1950) were able occasionally to visualize one or more of the coronary arteries in angiocardiographic examinations following the intravenous injection of Diodrast. The visualization was clearer in infants and chil-

dren when examined under an anesthetic. Pearl and associates (1950) devised an apparently safe method of coronary arteriography in the dog. They inserted a specially constructed catheter, through a peripheral artery, into the aortic sinus, injected 4 ml of 70 per cent Diodrast and regularly obtained the outline of the coronary arteries Electrocardiograms taken during the procedure were normal. The method, however, is still in the experimental stage (Helmsworth, 1951).

Infarction "at a Distance." When a branch of one coronary artery becomes obstructed, the portion of the myocardium which is rendered ischemic may then derive its nourishment principally from a branch of the other coronary artery, by development of anastomotic channels If now, the latter artery should become occluded, fresh myocardial infarction may result in the area normally and originally supplied by the first artery (Saphir *et al*, 1935). This has been called "ectopic" infarction (Bean, 1938) or "infarction at a distance" (Blumgart, 1939) Thus, following occlusion of the anterior descending branch of the left coronary, the nourishment to the apical portion of the left ventricle may be taken over by collateral circulation from the right coronary artery; if then the right coronary artery should suddenly become occluded, the apical portion of the left ventricle may suffer acute infarction. In other words the area of myocardium becomes infarcted owing to interruption of the blood supply furnished by the anastomosing channels of a collateral vessel.

Relation of Coronary Sclerosis to Disturbances in Conduction. Monckeberg (1924) pointed out that in infarction of the myocardium, the atrioventricular conduction bundle may be involved or spared, depending upon whether the independent blood supply to the bundle is involved.

Master and associates (1938) encountered intraventricular block, including bundle branch block, in 15 per cent of 375 cases of clinical acute coronary occlusion. The block affected the left bundle branch in one-half the cases, the right bundle branch in over one-fourth, and was intraventricular in one-fifth of the cases. They found that defective intraventricular conduction in coronary occlusion aggravates the prognosis; the mortality rate in such cases in their series was 42 per cent as compared to a rate of 23 per cent in patients with normal conduction. In 20 hearts, studied at autopsy, of subjects who had had evidence of complete or partial heart block during life, recent occlusion was present in the left coronary artery in seven, in the right in five, and in both arteries in the remaining eight. In addition one or more arteries had been previously occluded in 16 of the 20 hearts. In four-fifths of cases of bundle branch block, they found infarction of the ventricular septum. They attributed such heart block to septal infarction with simultaneous involvement of the atrioventricular conduction tissues and the bundle branch system. They also found intraventricular conduction had been present during life twice as often in patients whose hearts at autopsy showed gross septal infarction as in those in whom infarction did not involve the septum.

It may be mentioned that the right bundle branch is supplied almost exclusively by the septal branch (see Gross, 1921) of the left anterior descending artery, while the left bundle branch is supplied by branches from both coronary arteries. Master and associates found that occlusion of the right coronary artery led to bundle branch block of either type more often than was to be expected; they could not correlate the type of conduction defect with the vessel occluded or the location of the infarct. They explained persistence of normal conduction in association with septal infarction by the presence of adequate

collateral circulation in the septum, and attributed transient bundle branch block to temporary anoxemia.

Yater (1938) reviewed the literature on pathogenesis of bundle branch block and reported the detailed histopathologic findings in six hearts in which serial sections were made through the conduction system. In each heart there was fibrosis involving both right and left bundle branches. These lesions were related to disease of the coronary arteries, rheumatic, atherosclerotic or hypertensive Yater determined that the newer (American) terminology of bundle branch block is more clearly correct than the old one, that the designation indicates which branch is more seriously damaged; and that the right bundle branch is probably more often damaged as a result of rheumatic arteritis or myocarditis, while the left is usually affected by atherosclerosis or hypertension or both. Rasmussen and Moe (1948) found left bundle branch block associated with hypertrophy of the left ventricle five times as often as with a local lesion of the left branch of the bundle In their review of the literature on intraventricular block, Rosenman and associates (1950) could not correlate the histologic with the clinical findings When blocking lesions were present, they were usually bilateral.

Sites of Occlusion of the Coronary Arteries. In a study of myocardial infarction in more than 100 hearts, Mallory and associates (1939) found definite thrombosis of a coronary artery in 70 hearts. The number of instances of thrombosis in each vessel was as follows: left coronary artery, 59 (anterior descending branch, 52, circumflex branch, 4; septal branch, 3), right coronary artery, 8, and both arteries, 3 Hochrein (1941) tabulated the sites of occlusion of the coronary arteries in 530 autopsied cases representing the total number of cases analyzed in 13 different reports in the literature. The anterior descending branch of the left coronary was occluded in 68 per cent, the right coronary artery in 21 per cent, both of these vessels in 8 per cent and the circumflex branch of the left in 6 per cent. Grewin (1948) studied the necropsy reports of 100 consecutive cases of myocardial infarction, and found complete occlusion of the left anterior descending branch in 21 cases, of the right coronary in 14 and of the left circumflex branch in 7.



Figure VII-12 Closure of ostium of high-placed right coronary ostium by atherosclerotic plaque Heart was the seat of fresh infarction (Courtesy Dr J L Chason and Jerome Schleiffer, Veterans Administration Hospital, Dearborn, Michigan)

In the series of fatal cases of coronary artery disease reported by Yater and associates (1948c), the incidence of almost complete sclerotic occlusion (in 232 subjects) affecting the various vessels was as follows: left anterior descending, 192; left circumflex, 60; right coronary, 59. The incidence of thrombotic occlusion was as follows: left anterior descending, 174; right coronary, 49, left circumflex, 28. In the vast majority of cases the occlusion, whether sclerotic or thrombotic, involved only the proximal third of the affected vessel.

Pathologic Basis of Myocardial Infarction. In nearly all instances myocardial infarction is the result of occlusion of one or more coronary arteries (Figure VII-12).



Figure VII-13 Old organized coronary thrombus (sclerotic occlusion) with partial calcification and partial recanalization (WCGH, 38 A 241)

The commonest lesion is coronary atherosclerosis with occlusion or severe narrowing (Figure VII-13) at one or more locations. Frequently a fresh or recent thrombus is superimposed on the atheromatous lesion or develops just proximal to it. Occlusion may also be caused by syphilitic involvement of the coronary orifice, although infarction seldom results from this slowly developing process. Sudden coronary occlusion, such as caused by embolism or trauma or compression, or rupture of a coronary artery as by trauma or perforation of an aneurysm, is more likely to result in myocardial infarction. Occlusion from thrombosis occasionally occurs in rheumatic arteritis and rarely in thromboangiitis obliterans or polyarteritis nodosa.

Coronary Thrombosis Associated with Atherosclerosis. In practically every case thrombosis of the coronary artery develops on the basis of pre-existing atherosclerosis. In 46 hearts with myocardial infarcts, Levine and Brown (1929) encountered coronary thrombosis 23 times, each time on the basis of atherosclerosis; in 34 hearts with advanced coronary sclerosis, Saphir and associates (1935) demonstrated thrombi in 32, the thrombus in each instance being located on an atheromatous ulcer.

Traumatic Coronary Thrombosis with Myocardial Infarction. Instances of traumatic coronary thrombosis with fresh myocardial infarction are cited by Monckeberg (1924) and Moritz (see Chapter XI).

Bean (1937) encountered three instances of traumatic myocardial infarction among 9629 consecutive autopsies. One of these concerned a patient who fell 8 feet from a ladder, sustaining fractures of the ribs of the left side. He died ten weeks later and at autopsy a recent infarct with beginning aneurysm formation was present. H. Levy (1949) reported an example of traumatic coronary thrombosis with a myocardial infarct in a woman of 49 who had sustained a contusion of the chest wall in an automobile accident and died 13 days later. Autopsy revealed hemorrhage beneath the intima, rupture of the intimal lining and thrombosis in the lumen of the anterior descending branch of the left coronary artery, together with a large myocardial infarct involving the ventral half of the entire apex. The microscopic appearances of the thrombus and the infarct were consistent with changes which could occur in the interval between the accident and death. Friedberg (1949) states that in cardiac wounds the coronary arteries are commonly involved, particularly the anterior descending branch of the left coronary. In the application of non-penetrating blunt force to the chest wall, the ventral position of the right coronary artery is said (Helpern, 1949) to render this vessel more vulnerable to injury than the left artery.

Pathologic Considerations

Sites of Coronary Occlusion in Relation to Location of Infarcts. The sites of predilection for formation of atherosclerosis



Figure VII-14 Old apical infarct with mural-thrombus Cannulae inserted into mouths of coronary arteries preliminary to injection of radiopaque material (Courtesy Armed Forces Institute of Pathology, Acc No. 133726)

in the coronary arteries (see page 560) are the same for the development of superimposed thrombosis or of complete occlusion of the lumen The commonest site of occlusion is the anterior descending branch of the left coronary artery about 2 cm from its origin (Figures VII-14 and VII-15) The circumflex branch of the left coronary and the main stem of the right coronary are each involved much less often, a common site of occlusion of each of these vessels being about 1 cm from its origin.

Schlesinger (1938) has pointed out the consistent absence of large vessels and of fibrosis in the posterior basal portion of the right ventricle and the rarity of infarction in this location Despite the frequency of occlusion of the right coronary artery, infarction of the right ventricle is extremely rare. Blumgart and associates (1940) believe that this is so because the right ventricle, like the atria, is thin-walled and may derive considerable nourishment from the blood coming directly from its cavity.

Levine and Brown (1929) found that of 45 infarcted hearts, 39 (85 per cent) had infarcts which corresponded to the distri-



Figure VII-15. *Injected heart showing segmental narrowing of coronary arteries and their branches Note extreme narrowing of anterior descending branch about 2 cm from its origin.* (Courtesy Armed Forces Institute of Pathology, Acc 133726-254-10)

bution of the anterior descending branch of the left coronary, four to that of the left circumflex branch and two to that of the right coronary artery. In 49 hearts with old or recent infarcts studied by Barnes and Ball (1932) infarcts were located at the following sites, all in the left ventricle: anterior portion and apex (anterior apical infarcts) 28; posterior basal portion (posterior basal infarcts), 24; left posterolateral wall (midventricular infarcts) eight; and diffusely beneath the endocardium in three instances. The infarcts in these hearts were located at sites which were found to be supplied by the following arteries: anterior descending branch (28 instances), right coronary or a branch (20 instances) and circumflex branch of the left coronary (17 instances). Definite occlusion of these vessels was found as follows: anterior descending, 18; right coronary or branch, 9, and circumflex 7. As previously mentioned, Saphir and associates (1935) determined that, in the presence of a myocardial infarct, at least two branches of the coronary arteries supplying the infarcted area are occluded by atherosclerosis. In their series of 32 infarcted hearts, they found no instance in which only one main coronary artery was involved. In this series, when only extreme narrowing of the lumen was present,

without occlusion by atherosclerosis or thrombosis, at least three main branches were affected. In Bean's (1938) series of 287 infarcted hearts, the left coronary tree was seriously involved in 84 per cent, the right coronary tree in 21 per cent. In 54 infarcts studied by Mallory and associates (1939), the infarct was located in the left ventricle 53 times (apex 24, apex and septum 22, base 5, base and septum 2) and in the right ventricle once. In 2000 consecutive autopsies, Wartman and Hellerstein (1948) encountered 235 myocardial infarcts in the hearts of 160 subjects In 94 hearts, the infarcts were single and in 66 multiple. There were 134 hearts with infarcts in the left ventricle only; 18 with infarcts in both ventricles, 4, in the right atrium only; and 4, in the right ventricle only. In a series of 137 hearts studied by Yater and associates (1948c) there was a total of 153 myocardial infarcts (130 gross and 23 microscopic). The infarcts were located in the left ventricle and, or, the ventricular septum in all but seven instances These seven infarcts were located in the posterior wall of the right ventricle

According to Monckeberg (1924), the sites of predilection of necrosis and scarring are (1) the papillary muscles of the left ventricle; (2) the lower third of the anterior wall of the left ventricle, and (3) the upper portion of the posterior wall of the left ventricle

Infarction of the Atria. Cushing and associates (1942), in a postmortem study over a period of seven years, searched for atrial infarcts Among 182 consecutive hearts with myocardial infarcts they found 31 with atrial infarcts (17 per cent) In six hearts only the atrium was involved, in the other hearts, the atrial infarcts were associated with ventricular infarcts. The right atrium was involved in 27 hearts, the left atrium in five. Mural thrombi were associated with 26 of the 31 atrial infarcts. The clinical findings were generally not significant as regards atrial infarction; but in approximately two-thirds of subjects who had had electrocardiograms, there was some abnormal atrial mechanism. Of 66 atrial infarctions reported in the literature, rupture of the atrial wall occurred in three (Soderström, 1948)

Soderstrom, who made a thorough study of atrial infarcts, stated that they are to be expected in at least 1 per cent of hearts in an average autopsy material. He collected 192 hearts with mural thrombi in the atria and microscopically examined the adjacent atrial walls for evidence of infarction Right atrial thrombi were somewhat commoner than left atrial thrombi. In the right atrium they were commonly associated with coronary heart disease, in the left atrium they were usually associated with rheumatic heart disease In 46 cases he encountered infarcts in the right atrium and in one case an infarct of the left atrium. The rarity of left atrial infarcts is attributed mainly to the high oxygen tension in the blood within the lumen of this chamber. Ventral infarcts of the right atrium usually involved the auricular appendage, while dorsal infarcts of the right atrium were generally associated with, and an extension of, "posterior" infarcts of the left ventricle Atrial infarcts were difficult to recognize not only grossly but also histologically In the central zone of infarction, the necrosis is of hyaline type similar to that commonly seen in ventricular infarcts; in the marginal zone, the myocardial damage is less severe, apparently because in this area the myocardium derives some nourishment from the blood within the lumen of the chamber The myocardial fibers in the marginal zone are rich in glycogen, appear vacuolated, have few myofibrils, and are said to show "foamy degeneration." Of 66 atrial infarctions reviewed in the literature, Soderstrom found three reports of rupture of the atrial wall. None of the atrial infarcts in his series was

the seat of rupture, and in none of his cases could clinical symptoms be attributed to the atrial infarct.

In a study of the autopsy reports of 281 subjects with myocardial infarcts, McCain and associates (1950) found that the atrium was infarcted in 24, an incidence of 8.5 per cent; in 17 of the 24, the infarct was recent. Wartman and Souders (1950), in a careful study of 50 hearts containing a total of 72 infarcts, found infarcts in the atria in 21 hearts (42 per cent). These were located in the right atrium in 17, in the left in 2, and in both atria in 2, and they were always associated with ventricular infarcts. Most of them were fresh. They were thought to be a contributory factor in death.

Cardiac Lesions in Sudden Death from Coronary Insufficiency. As previously stated, in most instances of sudden death from coronary insufficiency, one or more coronary arteries are occluded, in a few cases the coronary arteries are relatively free of disease and in most of these the left ventricle is greatly hypertrophied, chiefly as a result of hypertensive disease. In most instances, the heart will reveal neither coronary thrombosis nor gross evidence of fresh infarction, but rather a severe degree of atherosclerosis at one or more points or diffusely, in two or all three of the main vessels. A precipitating factor (see page 584) is often present, but sometimes inapparent or absent. In the series of Yater and associates (1948c), only sclerotic occlusion was found in 175 of the 450 hearts, only thrombotic occlusion in 172, both sclerotic and thrombotic occlusion in 57, and neither sclerotic nor thrombotic occlusion in 46. In only one-fourth of the 450 hearts was gross evidence of myocardial infarction present.

If death ensues within a few hours after the onset of the acute attack of coronary insufficiency, no gross myocardial change may be evident. If death occurs after four or five hours or within a few days, the necrotic muscle may be deep red in color because of extravasation of blood, or clay-colored because of local anemia, and interspersed with or bordered by zones of red (hemorrhage) and yellow (fatty degeneration and leukocytic infiltration). After several days, with beginning organization the areas of myocardial necrosis may appear darker brown than the adjacent muscle, and soft, depressed and dry. The softness of the necrotic muscle was responsible for the old term "myomalacia cordis," introduced by Ziegler (1880).

Gross and Microscopic Changes in Experimental Infarction. Karsner and Dwyer (1916) ligated the descending ramus of the left coronary artery in dogs and sacrificed the animals at various intervals from one-half hour to 70 days. They described in detail the gross and microscopic myocardial changes. Grossly, the first recognizable change was pallor; after two days, the infarct was dry and granular; after five days, the infarct was sharply defined and surrounded by a fine line of reactionary hyperemia, after 61 days, fibrosis was complete but minute yellow necrotic areas were still to be seen. Microscopically, the changes noted after one-half hour were congestion, edema, small hemorrhages and decrease in cross-striations of myofibrils. Cloudy swelling of muscle was seen at one and one-half hours. At 12 hours, the muscle showed hyaline necrosis and the nuclei were pyknotic or had disappeared; polymorphonuclear leukocytes and a few mononuclear cells had infiltrated the area of necrosis. These changes were more pronounced at 24 hours, at which time mitotic figures were recognized in the perivascular and subendothelial connective tissue. Fatty degeneration appeared at 24 hours and remained until the necrotic muscle disappeared. The Anitschkow "myocyte" also appeared at 24 hours but was infrequent after five days. The muscle cells occasion-

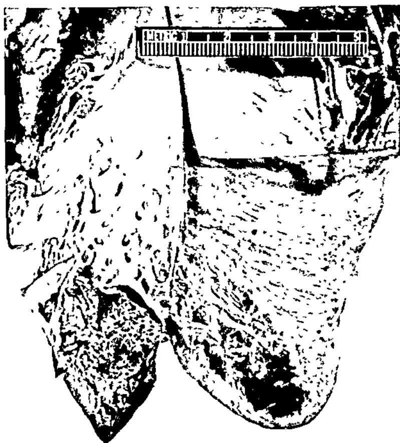


Figure VII-16 Old and fresh myocardial infarcts History of myocardial infarction six years before death, last attack, three days before death (WCGH, 49 A 483)

ally showed nuclei after 24 hours, later so-called muscle giant cells were seen, apparently formed by the accumulation of nuclei. These cells had to be distinguished from foreign-body giant cells. The latter appeared at the same time but persisted longer. At 48 hours, the fibroblasts had increased in number, and at five days they formed a well defined zone at the periphery of the infarct. At six days, plasma cells were present and a few persisted up to 70 days After 11 days, the necrotic muscle decreased in amount, being replaced by connective tissue At 18 days, a well defined scar was present but inflammatory cells remained After 61 days, the connective tissue was condensed, very minute areas of necrotic tissue were still present, but cellular infiltration had disappeared. No evidence was seen of true muscle regeneration.

It is probable that these changes in the dog proceed at a more rapid rate than would occur in myocardial infarction in man, since the metabolic rate in the dog is relatively greater than that of man. It has also been pointed out that the size of the infarct and the size of the heart are smaller in the dog and that the remaining collateral blood supply is better than in man because of the absence of severe arteriosclerosis.

Gross Changes in Man. Gross changes ordinarily do not develop for five or six hours after an acute attack. If extensive myocardial infarction is found at autopsy in a subject who has expired within an hour or two after the onset of an acute at-



Figure VII-17 Portion of fresh thrombus which occluded an atherosclerotic coronary artery Duration of infarction, two days. X 150. (WCGH, 40 A 485)

tack, the infarct must be related to conditions existing prior to the onset of the attack. The earliest change is a loss of lustre of the necrotic muscle This soon becomes pale, dry and somewhat swollen. The border of the infarcted and living muscle is usually irregular. Within a day or two the muscle assumes a clay color if the infarct is diffuse or a streaked yellow appearance if the infarct is patchy. The yellow color is explained by fatty degeneration of the necrotic muscle fibers and, at the border of necrotic areas, by infiltration with polymorphonuclear leukocytes, particularly within the first five or six days of the infarct. In patchy areas of infarction at this period, there may be a mixture of healthy and dead or dying muscle, fatty change from infiltrated leukocytes, and congestion or hemorrhage, with a corresponding variety of colors (Figure VII-16). There may be considerable liquefaction necrosis with disappearance of many muscle fibers, thus accounting for much of the loss of thickness of the myocardial wall after healing of large infarcts. The border of the infarct may be reddish because of hyperemia of adjacent vessels or hemorrhagic from extravasation of blood from these vessels; at the end of one week the reddish color may in part be explained by young granulation tissue. After the first week or ten days, the border becomes depressed owing to shrinkage following removal of necrotic muscle. The depressed zone becomes progressively wider and paler, and the granulation tissue is replaced by fibrous tissue and after two or three months by a white scar.

If the infarct extends to the epicardial surface a pericarditis develops which usually is largely fibrinous but may have some

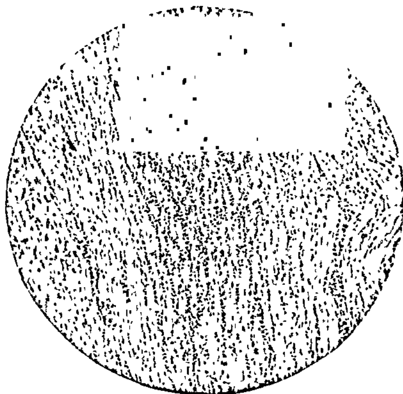


Figure VII-18 Acute inflammation at border of recent myocardial infarct Leukocytes are mainly polymorphonuclear Onset of attack two days before death. X 150 (WCGH, 40 A 485.)

hemorrhagic or purulent component, with survival of the patient, it heals by organization and scarring If the infarct extends to the endocardial surface, a thrombus usually forms at the site The resulting thrombus may cause narrowing of the lumen of the ventricle or the site of thrombosis may be marked by aneurysmal bulging of the ventricular wall

In hemorrhagic areas of infarction involving a good portion of the thickness of the cardiac wall ("cardiac apoplexy"), particularly if the epicardial surface is involved, there may be rupture of the wall with fatal hemopericardium In such cases, the entire thickness of the ventricular wall is usually infarcted. More often, however, infarcts undergo organization and are replaced by whitish scars, sometimes with a trace of pigment apparent. A patchy area of old scarring may be situated adjacent to, or be the site of, an organizing recent infarct (Figure VII-16), or of a new fresh infarct, either patchy or diffuse in distribution. These coexisting changes may be the result of progressive narrowing of one or more branches of the coronary arteries.

Microscopic Changes in Myocardial Infarction in Man. In an admirable report Mallory and co-workers (1939) described the microscopic changes in myocardial infarcts in the hearts of 72 persons in whom the onset of clinical findings enabled them to determine the age of the infarct Their microscopic findings may be summarized as follows:

1. *Necrosis of muscle, connective tissue and smaller blood vessels* Necrosis does not become evident for five or six hours, the muscle fibers then become hyaline and take a deeper acid stain, while the striations become less evident, the nuclei undergo pyknosis, karyorrhexis or karyolysis A layer of intact muscle, 0 3 to 0.5 mm

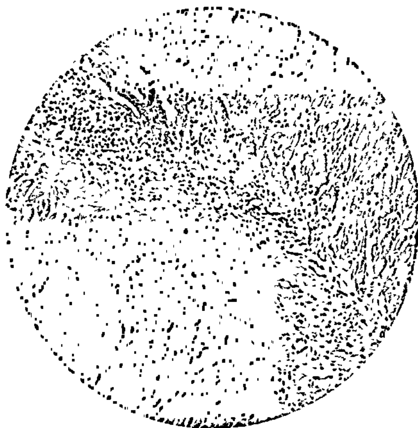


Figure VII-19 Portion of infarcted myocardium in person whose symptoms began 8 days before death Partially necrotic muscle fibers Young granulation tissue. Inflammatory cells are chiefly lymphocytes. X 150 (WCGH, 41 A 14.)

thick, usually persists beneath the endocardium, the nourishment for these fibers apparently being provided directly by blood in the cavity of the heart and in the thebesian veins.

2. *Hemorrhage* is usually focal rather than diffuse and extravasations are relatively rare The venules and capillaries are hyperemic. Hemolysis of erythrocytes results in deposition of hemosiderin which is phagocytized by macrophages. The infarction has features of both hemorrhagic and anemic types

3. *Fat* varies in amount depending on the suddenness of infarction and previous sufficiency of circulation. Most of the fat is found at the periphery of the infarct. The fat is removed by the macrophages at the same time as the necrotic muscle. As stated previously, the fat may represent dead or dying muscle fibers or an accumulation of leukocytes.

4. *Infiltration with polymorphonuclears* (Figures VII-17 and VII-18) begins at about five hours, starting at the edges of the lesion and spreading centrally. It is present in the interstitial tissue and about the blood vessels and gradually extends into the necrotic tissue At 24 hours, the infiltration of polymorphonuclears is slight, with beginning degeneration of leukocytes; at five days, many of the polymorphonuclears are necrotic; and thereafter they gradually disappear. Mallory and associates suggested that the polymorphonuclears may produce an enzyme which aids in the breakdown and phagocytosis of the muscle. *Eosinophilic polymorphonuclears* also are seen between the fourth and eighteenth days.

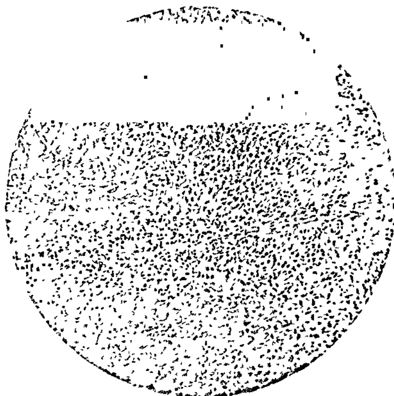


Figure VII-20 Organizing myocardial infarct, age 16 days X 150 (WCGH, 41 A 115)

5. *Ingrowth of blood vessels and connective tissue* Beginning on the fourth day new blood capillaries grow into the infarcted area, starting peripherally Fibroblasts accompany the blood vessels into the infarcted area (Figures VII-19, VII-20, and VII-21) The ingrowth is relatively greater on the epicardial than on the endocardial side If the infarct is large, the vascularization may not reach the center

6. *Removal of necrotic muscle. Infiltration by pigmented macrophages.* Simultaneously with the ingrowth of new capillaries and fibroblasts, macrophages invade and phagocytize the necrotic tissue. Occasionally giant cells may appear (Monckeberg, 1924) The fragments of muscle dissolve and disappear but their lipofuscin remains within the macrophages which become pigmented Some macrophages also contain hemosiderin which is produced from the breakdown of the red cells in areas of hemorrhage After about ten days, one millimeter of necrotic peripheral muscle has been removed, and after six weeks active absorption of necrotic muscle may still be present At two months, necrotic muscle fibers have generally been completely removed After one year practically all pigmented macrophages have disappeared. According to Monckeberg, one may occasionally see an attempt at muscle regeneration adjacent to the infarct.

7. *Lymphocytes and plasma cells* appear as soon as absorption of muscle starts, are fairly prominent during the third week and disappear about the same time as the pigmented macrophages Occasional mononuclear cells persist for many months.

8. *Collagen*, produced by the fibroblasts, appears first at twelve days, is prominent at three weeks and maximum at two to three months. The amount of collagen provides a good indication of the

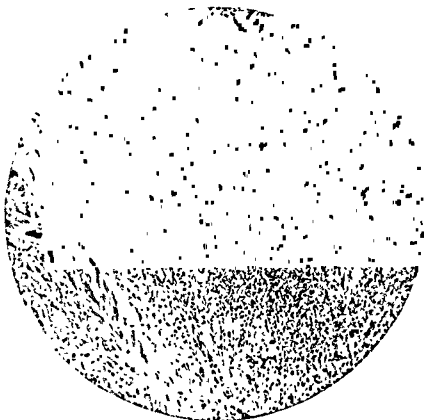


Figure VII-21 Portion of myocardial infarct History of acute attack 5 weeks before death X 150 (WCGH, 40 A 460)

age of the infarct. At six weeks the scar becomes contracted Adjacent to old infarcts the muscular fibers are often hypertrophic and their nuclei hyperchromatic (Monckeberg, 1924).

9. *Pericarditis.* Fibrinous pericarditis (Figure VII-22) appears within 24 hours. Organization of the exudate begins at eight days (or earlier) and is complete at four weeks. The pericardial reaction also provides a basis for judging the age of the infarct.

10. *Endocardial thrombus.* Thrombosis begins as early as five days but may occur much later. It is thought by some to be the result, not of the infarct, but of secondary dilatation of the infarcted wall. Its organization begins on the ninth day and complete organization may be present on the sixteenth day. Organization of the thrombus, however, is not a reliable guide in estimating the age of the infarct. Mallory and associates pointed out that, from the microscopic picture, the age of an infarct may be judged well during the first three weeks; that small infarcts heal more rapidly than large ones, that subendocardial infarcts heal less rapidly than those in the center of the myocardium or beneath the epicardium; and that the rate of healing depends on the competency of the remaining circulation and, therefore, on the degree of coronary arteriosclerosis, and on the amount of heart failure and anemia.

On the basis of their findings, Mallory and associates (1939) advised that patients with small or moderate-sized myocardial infarcts, without complications, be allowed one month of rest in bed, one month of carefully graded convalescence and a third month to consolidate recovery.

Myocardial Infarction with Coronary Occlusion. In most instances, myocardial



Figure VII-22 Acute serofibrinous pericarditis associated with fresh myocardial infarction, duration two days X 150 (WCGH, 40 A 485)

infarcts are associated with coronary occlusion. Plotz (1948) estimated that from 90 to 95 per cent of myocardial infarcts result from coronary sclerosis. Approximately one-half are associated with thrombotic occlusion alone, one-fourth with sclerotic occlusion alone, and one-fourth with both sclerotic and thrombotic occlusion (Yater *et al.*, 1948c). In most cases, all three main coronary vessels are involved by the atherosclerosis.

Myocardial Infarction without Coronary Occlusion. In Bean's series (1938) of 300 myocardial infarcts, 20 per cent were associated with arterial narrowing but no thrombosis. In four hearts the coronary arteries showed no significant damage.

Gross and Sternberg (1939) reported that in 15 hearts with extensive infarction (1 recent, 14 healed) the coronaries showed insignificant intimal changes and scant narrowing of the lumina. It should be pointed out that in 13 of these cases the patients had associated hypertension Twelve hearts weighed 350 Gm. or more and, in eight instances, the weight ranged from 470 Gm to 810 Gm Among 114 hearts with gross myocardial infarcts studied by Yater and associates (1948c), eight showed no complete occlusion of any artery. Wartman and Hellerstein (1948) in a study of 160 infarcted hearts found neither disease nor occlusion of the coronary arteries in 3.8 per cent. Such occurrences must be explained by prolonged relative myocardial ischemia The concept of relative ischemia as a cause of heart failure in hypertrophied hearts which reveal very little or no atherosclerosis, is not accepted by Harrison and Wood (1949). They maintain that focal myocardial fibrosis (indistinguishable from healed infarcts but unassociated with coronary occlusion) should be attributed to a diminution of coronary flow "during a

phase of cardiac failure" rather than to relatively small arteries or spasm. Karsner (1949) states that he has not seen myocardial infarction without organic occlusion of the coronaries.

Infarction of Muscle Bundles. Monckeberg (1924) states that there doubtless are instances in which scarring is confined to the inner or outer layer or involves the entire wall. He refers to Aschoff, who believed that the site of necrosis of the ventricular wall was always the middle layer. The ventricular muscle bundles have specific functions and apparently each has its own blood supply (Robb and Robb, 1942). The function of the superficial muscles is to fix the apical fulcrum and the atrioventricular valve leaflets, the function of the deep muscles is chiefly expulsive Lowe (1939) reconstructed myocardial scars in five hearts and decided that their position was consistent with one of the muscle groupings. He suggested that the scars represented a type of infarct which resulted from interference of blood supply to a portion of a muscle bundle rather than to coronary occlusion. Price and Janes (1943) described the occurrence of a large sheet-like subendocardial infarct (Figure VII-23) involving the posterior wall of the left ventricle from the base of the atrioventricular ring to the apex; it also included the posterior papillary muscle and the ventricular septum throughout its length and extended onto the anterior wall of the ventricle in the middle and distal portions. They thought that the infarct corresponded to a muscle grouping in the ventricle, that of the subendocardial portion of the superficial bulbospiral muscle, rather than to the distribution of a main coronary vessel.

Piram and Schlichter (1946) reported the occurrence of a large subendocardial infarct involving about two-fifths of the thickness of the left ventricular wall. The patient was an 82-year-old woman with severe coronary sclerosis but no recent or old occlusions. The infarct was judged to be between 24 and 36 hours old. This lesion may be regarded as representing the effect of an acute coronary insufficiency.



Figure VII-23 Scarring of old subendocardial infarct. (WCGH, 50 A 220.)

The patient also presented arteriosclerotic plaques in the aorta at the mouths of the coronary arteries; these were believed to be responsible physiologically for chronic coronary insufficiency and anatomically for moderate interstitial fibrosis of the myocardium.

Small myocardial scars (Figure VII-24) are usually to be attributed to occlusion of small branches of the coronary arteries, but in hearts with evidence of old rheumatic disease, it is possible that some of the scarring has been produced by the rheumatic disease (Karsner, 1949).

Wartman and Souders (1950), in a study of 50 hearts having a total of 72 myocardial infarcts, determined that the pattern of every infarct corresponded to that of one or more of the four principal muscle bundles of the heart (Figures VII-25 and VII-26). They classified their ventricular infarcts as full-thickness (entire thickness of ventricular wall), massive (but not full-thickness), and laminar or rim-like. The first two types commonly involved more than one muscle bundle, the last type usually involved only one bundle. Rupture occurred only in full-thickness infarcts, and aneurysm and mural thrombosis were more likely to occur in such infarcts.

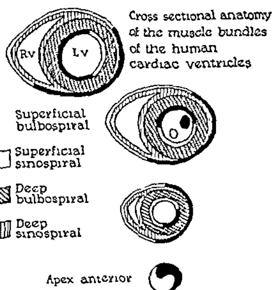


Figure VII-25 Localization of myocardial infarcts with respect to muscle bundles of the heart (From Wartman, W B, and Souders, J C Localization of myocardial infarcts, *Arch Path*, 50 329-346, 1950 Courtesy of the authors and *Archives of Pathology*)



Figure VII-24 Small myocardial scar of infarct resulting from closure of small branch of anterior descending coronary artery (WCGH, 49 A 44)

The superficial bundles were involved, either alone or in combination with a deep muscle, in 74 per cent of infarcts, the deep bundles were involved, alone or in combination with a superficial muscle, in 51 per cent. The deep sinospiral bundle was affected significantly less often than any other muscle. The right ventricle, which is composed largely of the deep sinospiral muscle at the base and of the superficial and deep sinospiral muscles at the apex, was seldom infarcted. The basal two-thirds of the heart is composed chiefly of deep bundles and the apical third of the left ventricle is made up entirely of superficial muscles. Wartman and Souders encountered infarcts involving more than on bundle much more often than infarc

single bundle, the prognosis is worse in the former condition than in the latter.

Fever, Leukocytosis and Increased Sedimentation Rate. In myocardial infarction, fever, leukocytosis and increase in the sedimentation rate of blood cells are almost always present, singly or in combination, beginning during the first 24 hours.

Rabinowitz and associates (1931) found that fever and leukocytosis usually appear earlier than increase in sedimentation rate but that the increased sedimentation rate persists longer. In several of their patients on whom these tests were made on the day following the onset of the attack, the sedimentation rate was normal but fever and leukocytosis were already present.

Fever may not be detected unless the temperature is taken rectally The average leukocyte count is 12,000 to 15,000 and counts of over 30,000 are rare. An unusually high leukocyte count and the finding of over 30 per cent of nonfilamented polymorphonuclears after the fourth day are regarded as unfavorable signs (Goodrich and Smith, 1936). Koenig and Young (1947) have pointed out the importance of following a series of daily determinations of the sedimentation time during the first days following infarction. The most rapid increase in sedimentation time occurs four or five days after the onset of the attack. The rate may not return to normal for several weeks or several months.



Figure VII-26. Transection of the heart near the base showing white laminar scar of an old posterior basal and lateral infarct of the subendocardial portion of the superficial bulbospiral muscle. External to this scar are dark rim-like fresh infarcts of the deep bulbospiral muscles. These new infarcts are actually parts of a single infarct. (Courtesy of W. B. Wartman and J C Souders and *Archives of Pathology.*)

Increase in Serum Mucoprotein Following Myocardial Infarction. An increase in the level of serum mucoprotein after infarction was consistently found by Simkin and associates (1949). In 23 patients with recent infarction, increases of from 22 to 160 mg. above their previous normal ranges (40 to 90 mg. per 100 ml.) were noted beginning on the third day and usually reaching a peak on the sixth day This level was maintained for another week, after which it declined. The mucoprotein was not specific for breakdown of cardiac protein, since elevations in its value were obtained in patients after operations, and in those with cancer and pneumonia. No relation was found between the level of the mucoprotein and the sedimentation rate. It was believed that the changes in serum mucoprotein are a more accurate indication of the presence or absence of a recent myocardial infarction than are the sedimentation rate and the leukocytic count.

Multiple Attacks of Infarction. Feil and associates (1938) found multiple acute infarcts (Figure VII-27) without previous infarction in eight of 34 patients who died of recent infarction. Master and associates (1937) obtained a history of previous coronary occlusions in approximately one-half of their patients. The frequency of attacks may be judged from the mortality rate in their patients, 11 per cent of their patients died in the initial attack, 29 per cent in the second attack and 50 per cent in the third attack. In the series of Yater *et al.*



Figure VII-27 Multiple old myocardial infarcts, *one* with ventricular aneurysm and organizing laminated mural thrombus (WCGH, 101-36)

(1948c), in 14 of 114 soldiers, the heart had two infarcts and in 2, three infarcts. Wartman and Hellerstein (1948) found a total of 235 myocardial infarcts in 160 patients· 196 (83 per cent) in the left ventricle, 22 in the right ventricle, 15 in the right atrium, and two in the left atrium The left ventricle was involved in 152 of the 160 hearts Among 94 hearts with single infarcts, the process was recent in 50 and old in 44, among 66 hearts with multiple infarcts, the lesions were recent in 10, old in five, and both recent and old in 51.

Cause of Death in Myocardial Infarction. The commonest cause of death in myocardial infarction is a thrombotic or embolic lesion. Such lesions account for approximately one-third of deaths. Other common causes are progressive circulatory failure, shock and cardiac rupture. In cases of sudden death *in* which no other lesion *is* demonstrable, death is presumed to have been caused by a disturbance in the conducting mechanism, such as heart block or ventricular fibrillation. In most instances cerebral infarction, occurring in patients who have had a recent myocardial infarct, *is* not the result of an embolus from a mural thrombus but rather is the result of a thrombus that develops in an atherosclerotic cerebral artery. The presence of a myocardial infarct appears to favor coagulation of blood and secondary thrombosis in other organs (Hellerstein and Martin, 1947).

Sequelae of Myocardial Infarction

Sudden death during or following an attack is caused in most instances by *shock* or by *arrhythmia,* presumably ventricular fibrillation (Selzer, 1948). Those who survive the immediate attack may develop *left ventricular failure* or may die later from arrhythmia or from *embolism* to the arteries of the brain, lung, mesentery or extremities, or from recurrent coronary occlusion Occasionally right ventricular failure supervenes and this may be further complicated by the occurrence of *pulmonary embolism* (from systemic veins or right side of heart) or pneumonia. Blumgart and co-workers (1940) concluded that death results whenever a sufficiently large area of myocardium undergoes ischemia, with or without necrosis, or when because of ischemia, there ensues asystole, ventricular fibrillation or congestive failure

Pericarditis. The incidence at autopsy of pericarditis following infarction varies considerably in different series of cases, as may be seen by the following figures. Yater and associates (1948c), 15.5 per cent; Wartman and Hellerstein (1948), 28 per cent; Bean (1938), 32 per cent, Feil, Cushing and Hardesty (1938), 62 per cent, and Stewart and Turner (1938), 80 per cent. In Bean's series, an effusion of 50 ml. or more was present in 15 per cent, hydrothorax was frequent and usually was greater on the right side In the series reported by Stewart and Turner, pericarditis when present was localized in 75 per cent of cases and generalized in the others. The pericarditis is, of course, the result of extension of the infarction to the epicardial surface.



Figure VII-28 Old myocardial infarct with mural thrombus at site of aneurysmal dilatation of ventricle Severe sclerosis and narrowing were present in the anterior descending branch of the left coronary artery. (WCGH, 45 A 172)

Mural Thrombosis. Until recent years, mural thrombi were encountered at the site of infarction in approximately 50 per cent of infarcted hearts (Blumer, 1937; Bean, 1938). Since the introduction of anticoagulant therapy (Dicumarol or heparin) in the treatment of patients with acute myocardial infarction, the incidence of mural thrombosis as well as of secondary embolism which follows mural thrombosis has been significantly reduced (Wright *et al.*, 1948; Schilling, 1950). Although mural thrombi usually form as a result of extension of the infarct to the endocardium, they may also form as a result of localized dilatation of the infarcted wall (Figure VII-28). Bean found some thrombi still remaining three years after the acute infarction. As would be expected, mural thrombi are found most frequently, in association with myocardial infarction, in the left ventricle. They occur less often in the atria and least often in the right ventricle. In 46 cases of recent myocardial infarction studied by Levine and Brown (1929), there was gross evidence of mural thrombosis in 38 and of pericarditis in 24; only three hearts showed no gross evidence of either mural thrombosis or pericarditis.

Embolism or Systemic Thrombosis Following Mural Thrombosis. Systemic embolism occurs in approximately one-third of patients having mural thrombi in the left ventricle and appears to be particularly frequent when the thrombus is attached to the ventricular septum (Bean, 1938). The commonest sites of embolism in order of frequency are lungs, kidneys, spleen, brain, lower extremities (femoral arteries) and intestines (mesenteric arteries).

Pulmonary embolism is the most frequent form of embolism occurring in patients with myocardial infarction, but it is less serious prognostically than embolism to the brain or to a large vessel of an ex-

tremity (Blumer, 1937). Pulmonary emboli take their origin principally from veins of the pelvis or lower extremities, particularly in instances of massive pulmonary infarction, they may also arise from mural thrombi in the right side of the heart.

Cerebral infarction develops in patients with myocardial infarcts more often as a consequence of cardiac failure than as a result of embolism from a mural thrombus. Bean and Read (1942) reported 8 instances of acute myocardial infarction in subjects having associated central nervous system manifestations (coma in four patients, hemiplegia in two patients). At autopsy severe cerebral arteriosclerosis was present but no evidence of embolism, thrombosis or hemorrhage They attributed the symptoms to congestive heart failure with fall in blood pressure, reduction in circulation and anoxia of brain. Recurring transitory hemiparesis is attributed by Bean and associates (1949) to restricted blood flow rather than to vascular spasm

Scheinker (1951) has emphasized that acute damage to the brain may result from sudden fall in arterial blood pressure in myocardial infarction As a result of reduction in blood supply to the brain, ischemic changes may develop in the cortical gray matter, basal ganglia or medulla, and the white substance may become swollen. The leptomeninges may reveal pronounced passive hyperemia and venous thrombosis while the brain substance may be the seat of hyperemia of the smaller veins and capillaries, perivascular edema or petechial hemorrhages The resulting functional changes may be mild or serious, transitory or protracted, depending on the severity and duration of the basic physiologic disturbance in the heart.

Hadorn (1938) reported the occurrence of sudden death from embolism into the same coronary artery in which an earlier thrombus had resulted in myocardial infarction and secondary mural thrombosis. Ravdin and Wood (1941) reported successful removal of a saddle thrombus of the abdominal aorta in a physician, aged 32, 11 days after an attack of acute myocardial infarction. It must be borne in mind that the incidence of thrombosis and embolism, as given above, will be greatly decreased with the use of anticoagulants in the modern treatment of myocardial infarction.

Rupture of Heart. Rupture of the cardiac wall at the site of fresh or recent infarction occurs in approximately 8 per cent of cases. Among mental patients, however, Jetter and White (1944) found a much higher incidence of rupture of hearts with acute infarction. In a series of 115 consecutive autopsies of mental patients who died suddenly or unexpectedly, 22 were found to have acute myocardial infarction. Sixteen of these (73 per cent) showed rupture of the cardiac wall at the site of the infarct. Most of these subjects had chronic mental illness with intellectual deterioration. The commonest site of rupture is the lower third of the ventral wall of the left



Figure VII-29. Fresh anterior apical infarct involving entire thickness of ventricular wall, with rupture. [illegible]

ventricle (Figure VII-29) just above the apex (Monckeberg, 1924).

Krumbhaar and Crowell (1925) reviewed the literature of the preceding fifty years on spontaneous rupture of the heart. To 632 published cases, they added 22 others. They emphasized that cardiac rupture nearly always occurs in an acute myocardial infarct which is the result of occlusion of a coronary artery. Rupture occurred more often in men (58 per cent) and in persons 60 years or older (72.5 per cent). Among persons under 45 years, with cardiac rupture, the incidence of syphilis was relatively higher than among older subjects; also rupture of the wall of an atrium was more frequent. In most instances the rupture was of the left ventricle (80 per cent), probably because disease of the anterior descending branch of the left coronary artery was responsible for the infarct, and because of the relatively high pressure within the left ventricle; other sites included the right ventricle (10 per cent), the right atrium (6 per cent) and the left atrium (2 per cent). Of the left ventricular ruptures, 60 per cent involved the ventral wall, 23 per cent the dorsal wall and 15 per cent, the apex. Usually the tear was 1 to 2 cm. long, the edges irregular or jagged, and the external opening larger than the internal opening. In most instances, the rupture was associated with the presence of excessive epicardial fat, and generally the heart was enlarged.

In a review by Edmondson and Hoxie (1942) of the protocols of 72 cases of cardiac rupture, rupture occurred in all portions of the heart except the dorsal wall of the right ventricle. This latter area is rarely the seat of infarction. Clowe and associates (1934) reviewed 34 cases of atrial rupture in the literature; of these 48 per cent occurred before the age of 40 as compared to only 7 per cent of ventricular ruptures occurring before 40. In all but 2 of 40 ruptured hearts studied by Benson and associates (1933) the infarction was on the basis of sclerosis, thrombosis or embolism of the coronary arteries; one was probably of syphilitic origin and one, a dissecting aneurysm involving the sinus of Valsalva, was due to endocarditis caused by *Streptococcus viridans*. Rupture may occur as early as one day and as late as four weeks after onset of infarction, but is commonest during the first week. The average time of occurrence is seven days. If rupture occurs three or more weeks after infarction, it is likely that a complication is present such as another acute infarct (Mallory *et al.*, 1939). Following perforation into the pericardial sac, death is usually sudden or occurs after a few minutes. In 90 per cent of 400 cardiac ruptures, the time of survival was twelve hours or less after onset of rupture (Krumbhaar and Crowell, 1925). In the case of ventricular septal perforation, survival is often longer, varying usually from several hours to several days, sometimes the patient survives for several months or years. The patient of Wood and Livezey (1942) lived nearly five years following this complication. Rupture of the ventricular septum may be diagnosed during life (Fowler and Failey, 1948) on the basis of the history and findings of myocardial infarction and the development of signs of a ventricular septal defect, and particularly the sudden appearance of a thrill and a loud harsh systolic murmur along the lower left sternal border; and of right ventricular failure. The condition which may be confused with rupture of the ventricular septum is rupture of a papillary muscle of the left ventricle following myocardial infarction; in rupture of the papillary muscle the murmur is louder and nearer the apex and there is left ventricular failure. Carroll and Cummins (1947) reported in a 60-year-old man with coronary occlusion and myocardial infarction, rupture of interventricular

septum followed by rupture of the posterior wall of the left ventricle.

Predisposing causes of cardiac rupture are absence of old myocardial scars and presence of heavy infiltration of leukocytes, hemorrhage and increase in subepicardial fat in the region of infarction, and undue exertion or persistence of hypertension after onset of infarction. Edmundson and Hoxie believe that old scar tissue in the region of fresh infarction may lessen the chance of perforation because of the presence in the scarred areas of increased collateral circulation and because of greater resistance of the fibrous tissue to ischemia and the support it gives to the necrotic muscle Howell and Turnbull (1950), however, were able to demonstrate old infarcts in 4 of 8 hearts that ruptured following acute infarction The accumulation of leukocytes in the infarcted myocardium may conceivably liberate proteolytic en-

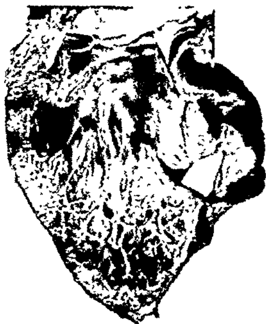


Figure VII-31 Large defect in interventricular septum at inferior portion of old posterior basal aneurysm The defect measured 2 cm in diameter and its walls were smooth. The defect in the upper portion of the figure was made by the cutting knife (Courtesy of Dr J L. Chason, Veterans Administration Hospital, Dearborn, Michigan)



Figure VII-30 Perforation of interventricular septum in area of old and recent infarction The walls of the defect were undergoing organization and a thrombus was attached to the inferior portion of the defect. (Courtesy of Dr J L Chason, Veterans Administration Hospital, Dearborn, Michigan)

zymes which may contribute to softening of the necrotic muscle and thus add to the danger of rupture. According to Lowe (1947), perforation is not likely to occur in a direct line but rather to follow the interfaces between the spiral muscles Rupture occurs in full-thickness infarcts, these are common at the apex of the left ventricle, which is composed entirely of superficial muscle bundles, and rare at the base of the heart, which is chiefly composed of deep muscles (Wartman and Souders, 1950).

An old healed septal defect following perforation of the infarcted septal muscle was reported by Gross and Schwartz (1936) to be circular and to have measured "several" centimeters in diameter and to have smooth regular edges (See Figures VII-30 and 31.)

McNamara and associates (1937) reported cardiac rupture from weakening of

myocardium by metastatic carcinoma. dden (1943) collected from the litera- 9 cases of myocardial abscess with liac rupture and added one case. None he 10 patients had any cardiac symp- is prior to the rupture.

[H]emopericardium. The commonest se of hemopericardium is rupture of the ocardium. Other common causes in- le trauma, and perforation into the icardial sac of a dissecting aneurysm of first portion of the ascending aorta. nopericardium is also found in some in- ices of metastatic neoplasms involving pericardium. In fatal hemopericar- m from tamponade following rupture the myocardium, the amount of blood the pericardial cavity has been esti- ted to vary from 150 to 700 ml., and in majority of cases from 200 to 250 ml dmondson and Hoxie, 1942) Munck 46) found an average volume of 380 ml. sanguineous fluid in the pericardial sac 16 cardiac perforations among men, and average of 270 ml. of fluid in 10 women. e slower the escape of blood into the icardial cavity, the larger the amount t can be tolerated In chronic disorders, e tuberculous pericarditis, as much as a er or more of fluid (not necessarily ody) may accumulate gradually, the art having had time to adjust itself to the eat distension of the pericardial sac

Ventricular Failure Following Myocar- al Infarction. Most patients with left art failure also develop insufficiency of e right ventricle, the manifestations of ich then dominate the clinical picture ishberg, 1932) This may occur especi- y in patients who, in addition to the left art failure, have chronic pulmonary dis- se and right ventricular hypertrophy. ilure of the right ventricle is particularly ely to ensue following perforation of the farcted ventricular septum. In this case e right ventricle must withstand the gher pressures transmitted from the left ventricle with which it communicates.

[illegible]

the left ventricle. In myocardial infarction with failure the primary strain is usually on the left ventricle, the right ventricle being secondarily affected.

Encroachment of the ventricular septum upon the cavity of the right ventricle, as in hearts with severe left ventricular hyper- trophy or in infarction of the septum, has sometimes been held responsible for the so-called Bernheim's syndrome, in which the patient develops symptoms of right heart failure with distention of the veins of the neck and injection of the facial veins, followed by cyanosis, edema of the lower extremities and congestion of the liver, but without accompanying pulmonary edema. Peel (1948) reported a dissecting aneu- rysm of the ventricular septum second- ary to calcification of the coronary arteries and thrombotic occlusion of the an- terior descending branch of the left coronary. The aneurysm formed a swelling 38 × 28 mm. and projected into the cavity of the right ventricle (Bernheim's syn- drome) for a depth of 15 mm. The progres- sive right ventricular failure in this patient was attributed, in part, to obstruction of the outflow tract of the right ventricle by protrusion into it of the septal aneurysm and, in part, to disease of the myocardium. Evans and White (1948), in a study of the clinical and pathologic findings in 33 sub- jects in whom the heart weighed more than 750 grams, did not encounter a single un- questionable example of "Bernheim's syn- drome" and recommended that the desig- nation be dropped. Fishberg (1940) and others (Atlas *et al.*, 1950; Russek and Zoh- man, 1950), however, support the validity of this syndrome. The development of car- diac hypertrophy as a result of cardiac failure that follows myocardial infarction has been previously mentioned (page 572).



Figure VII-32. Rupture of posterior papillary muscle of left ventricle. Heart weight 1025 Gm A "rising" systolic apical murmur was transmitted to the anterior axillary line Patient, aged 40, was in severe congestive failure during the last six weeks of his life (WCGH, 34 A 64)

Spontaneous Rupture of Papillary Muscle. Davison (1948) reviewed the clinical and pathologic findings in 31 reported *cases of spontaneous rupture of papillary* muscles Rupture of the papillary muscles of the right ventricle was encountered only twice, both as a result of involvement by bacterial vegetations Among instances of rupture of the papillary muscles of the left ventricle, the posterior muscle (Figure VII-32) was affected twice as often as the anterior In two instances perforation appeared to have been caused by syphilis; all others were associated with coronary arteriosclerosis and most of these with coronary occlusion and myocardial infarction. His own three cases were encountered among 14,000 autopsies, and in one of these, the diagnosis had been made antemortem. Davison ascribed the greater frequency of involvement of the posterior muscle to its remoteness from the source of blood supply, and perhaps to a poor collateral blood supply to the superficial bulbospiral muscle which forms the left posterior papillary muscle On the other hand, the left anterior papillary muscle is a favorite *site of scarring* (Monckeberg, 1924, p. 397). The left anterior papillary muscle derives its blood supply only from the left coronary artery (from a branch of the left anterior descending ramus) and lies at the greatest distance from the ostium of the artery (Gross, 1921), the left posterior muscle receives branches from both coronaries.

Smith (1950) reported two instances of spontaneous rupture of the left posterior papillary muscle in its midportion, associated in each instance with recent thrombosis of the right coronary artery. Each patient died in circulatory collapse three days after the onset of the attack. Smith states that in 18 of 33 reported cases, the rupture was the result of thrombosis of a coronary artery and was associated with infarction of the myocardium, the posterior muscle of the left ventricle wa

13 subjects, in 11 of whom there was thrombosis of the right coronary artery or of the circumflex branch of the left coronary. Rupture of the anterior papillary muscle of the left ventricle followed coronary. Rupture of the anterior papillary of whom the left circumflex or anterior descending branch was involved and in two, the right coronary.

Most patients die suddenly and almost immediately after rupture of a papillary muscle. In one patient, life persisted 10 months following rupture, in another, 20 months. One patient stated that he believed a muscle had broken over the heart. (See Stevenson and Turner, 1935.) The diagnosis may be considered in a patient with evidences of myocardial infarction if he develops a change in the character and intensity of a murmur which antedated the infarction. The new murmur is usually located over the mitral area, is systolic in time and loud and harsh in character. The condition must be distinguished from rupture of mitral chordae tendineae, rupture of an aortic cusp and acute perforation of an infarcted interventricular septum or ventricular wall.

Traumatic rupture of the papillary muscles has also been reported (Glendy and White, 1936, Payne and Hardy, 1937) and Smith (1950) mentions an unreported case in which rupture was attributed to polyarteritis nodosa.

Abscess Formation in Myocardial Infarct. Miller and Edwards (1951) reported the occurrence of an abscess in an acute myocardial infarct. The infecting organism, *Escherichia coli*, was believed to have been derived from the right kidney which was the seat of an acute pyelonephritis. The authors encountered reports of 3 other cases of abscess associated with acute myocardial infarct; in each of these the abscess was believed to have been a complication of a pyogenic pneumonia, and in one of these (Case 1, Tedeschi *et al.*, 1950) the heart had ruptured.

Rupture of Coronary Sinus. Hinshaw and Brown (1949) reported rupture of the coronary sinus as a result of involvement of the sinus in an area of recent myocardial infarction at the base of the lateral wall of the left ventricle, following atherosclerotic occlusion of the left circumflex artery near its origin.

Trophic Changes in Hands Following Myocardial Infarction. In 18 patients with clinical thrombosis and in 4 others with persistent angina pectoris, Askey (1941) observed a syndrome of pain and restriction of movements of one or both shoulders and of stiffness, pain and swelling of one or both hands. Seven of the patients had Dupuytren's contracture. The syndrome was explained by a reflex induced by myocardial ischemia, afferent fibers for painful stimuli from the heart connecting with afferent fibers for pain from the shoulder. Kehl (1943) reported six cases of Dupuytren's contracture (bilateral in five) as a sequel to coronary occlusion, and regarded irritation of the sympathetic ganglia as a consequence of the coronary disease to be a possible factor. Johnson (1943) observed disabling changes in the hands resembling sclerodactylia in 39 of 178 consecutive cases (21 per cent) of acute myocardial infarction, and suggested that they were caused by ischemia of the tissues of the fingers resulting from reflex vasoconstriction of the arteries of the hand induced by cardiac pain.

Aneurysm of Ventricle. A cardiac aneurysm represents bulging of a diseased weakened cardiac wall in response to the intraluminal pressure. About 85 per cent of such aneurysms are caused by coronary occlusion (Sternberg, 1914). Cardiac aneurysms most often involve the left ventricle, those of the right ventricle being rare, and those of the atria exceedingly rare



Figure VII-33 Large left ventricular aneurysm (WCCH, 47 A 301)

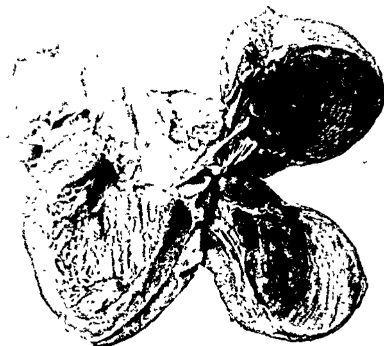


Figure VII-34 Section of left ventricular aneurysm (same as Figure VII-33) showing large laminated mural thrombus



Figure VII-35 Old posterior basal infarct with aneurysm of wall. Also note fresh occlusion with hematoma in left circumflex artery with fresh patchy hemorrhagic infarction of lateral wall of left ventricle (WCGH, 37 A 337.)

(Monckeberg, 1924). Anterior apical aneurysms (Figures VII-33 and VII-34) show bulging of an infarcted area that is generally 3 to 5 cm. or more in diameter, while posterobasal aneurysms (Figure VII-35) produce a lesser degree of bulging in an infarcted area and generally measure 2 to 3 cm. in diameter In the case reported by Shennan and Niven (1925), the greatest diameter of the aneurysm was 16 cm.

Among 160 myocardial infarctions, Wartman and Hellerstein (1948) found 35 (22 per cent) with ventricular aneurysm, all in the left ventricle. Of this number 25 were in the anterior apical portion, three in the posterolateral portion and seven in the posterobasal region. Most of the aneurysms had mural thrombi. Among 114 hearts with gross infarcts, Yater and associates (1948c) encountered four with ventricular aneurysms (3.5 per cent). Two of these aneurysms were the result of fresh infarcts and two the result of old infarcts. Betsch (1945) found eleven cardiac aneurysms among 141 cases of myocardial infarction (8 per cent); while Parkinson and associates (1938) determined from published postmortem statistics of six separate groups of observers that cardiac aneurysm occurred in 9 per cent of cases of infarction Among 7200 autopsies Betsch found an incidence of 1.5 per 1000 autopsies; Lucké and Rea (1921) found an incidence of 1.1 per 1000 in a series of 12,000 autopsies.

Fujinami (quoted by Monckeberg, 1924) reported occurrence of three ventricular aneurysms in a 75-year-old woman with severe atherosclerosis.

Ventricular aneurysms of arteriosclerotic etiology appear to develop particularly during the period of myocardial necrosis and softening, especially during the first two weeks after coronary occlusion (Fulton, 1941). Ball (1938) expressed the belief that the development of a ventricular

aneurysm is favored by permitting the patient to be up and around too soon, *i.e.*, within a week or two after the development of acute infarction. Evidence to support this belief is found in the work of Sutton and Davis (1931). These investigators exercised dogs following coronary ligation, and sacrificed the animals after an interval sufficiently long to permit healing of the myocardial infarct. One animal was given a rest of six days after ligation; the infarcted area was well scarred without thinning of the ventricular wall. In four other animals exercise was started within three days of the operation, their hearts presented thin scars with aneurysmal bulging.

Penner and Peters (1946) reported survival of 15 years following onset of occlusion, they believed that the aneurysm of the left ventricle was present for 15 years His long survival was attributed to an extended period (one year) of hospitalization after onset of symptoms of infarction Joachim and Mays (1927) encountered a large left ventricular aneurysm in a man of 25 who died suddenly, occlusion was found of the anterior descending branch of the left coronary artery near its origin. The patient had suffered multiple fractures of the ribs of the left side when he was run over by a wagon at the age of 12.

Parkinson and associates reported ventricular aneurysm following necrosis of the myocardium caused by rheumatic fever Cardiac aneurysms may also be caused by gumma, infective endocarditis with abscess of the myocardium, particularly in association with mycotic coronary arteritis, congenital defects and trauma.

Grossly the aneurysm may be saccular but more often it is not sharply demarcated from the ventricular cavity The endocardial surface is frequently the seat of a mural thrombus. The wall of the aneurysm, exclusive of any mural thrombus which may be attached is thinner than that of the ventricle prior to infarction. Its thickness is determined by the amount of muscle destroyed, the extent of scarring and contraction of scar tissue and the degree of bulging caused by the intraventricular pressure Monckeberg (1924) pointed out that adhesions between the epicardium and pericardium in the region of the aneurysm may serve as a protective measure against an otherwise fatal hemorrhage into the pericardial cavity

Microscopically the muscle fibers are decreased in size and often in number, and there are various degrees of necrosis, fibrosis, hyalinization and, sometimes, deposits of calcium in the infarcted area The degree of myocardial softening seems to be a predisposing factor in spontaneous cardiac rupture following myocardial infarction (Edmondson and Hoxie, 1942).

The larger ventricular aneurysms may be diagnosed clinically on the basis of a history of coronary occlusion, electrocardiographic changes, enlargement of the heart, particularly to the left, changes in the character of the apical pulsation, and radiologic examination, indicating alteration in size, shape and contour of the heart. In anterior aneurysms, a "ledge" or bulge (Figure VII-33) in the cardiac border may be seen on x-ray examination when the patient is placed in the right oblique position, while posterior aneurysms (Figure VII-35) may sometimes be seen with the patient in the left oblique position. Aneurysm or perforation of the interventricular septum may cause enlargement of the heart to the right. Sometimes calcification occurs in the wall of an aneurysm and may be seen in roentgenograms. On fluoroscopic examination, an aneurysm located between the apex and the base may produce a localized area of pulsation in this area.

Calcification of Myocardium may be the result of inflammatory, toxic or vascular lesions Plaque-like areas of calcification

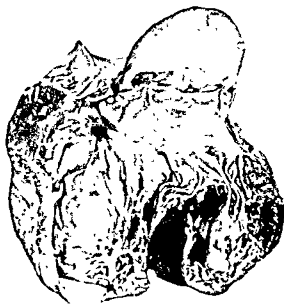


Figure VII-36 Old infarct and aneurysm involving lower two-thirds of right ventral wall of left ventricle and lower and ventral three-fourths of septum Patient was a man of 68 who died from effects of carcinoma of prostate rather than from heart disease (WCGH, 38 A 361)

may be found (principally by radiologic examination) in old myocardial infarcts and particularly in the wall of an aneurysm (Brean *et al*, 1950). Calcification must be distinguished from that occurring in the pericardium as a result of an old tuberculous or purulent inflammation. Finestone and Geschickter (1949) briefly reviewed the literature on myocardial calcification and found that the commonest lesion in which calcification occurred was an old myocardial infarct In addition to their own case, they mentioned five others in which bone formation was associated with the calcification (See Figure VII-37.)

Spontaneous Rupture of Cardiac Aneurysm. Spontaneous rupture of a cardiac aneurysm is rare, the usual terminal event being cardiac failure; rupture of the heart wall following coronary occlusion is more likely to occur during the first 10 days after onset of the infarction.

Betsch (1945) reported two instances of spontaneous rupture among 11 subjects with cardiac aneurysm. Betsch's first case was a 40-year-old man whose first attack of infarction occurred four months before death. He had a ventricular aneurysm, 10 cm. in diameter, which still showed an organized mural clot. In his second case the aneurysm occurred in a 52-year-old man with no previous cardiac history and appeared to be of recent origin. Fisher's (1945) patient was 67 years of age and died of rupture of a cardiac aneurysm eleven weeks after onset of symptoms of infarction. This patient appeared to have had adequate rest following the myocardial infarction. Almost always rupture of the heart occurs in a fresh myocardial infarct but Brown and Evans (1940) reported an instance of cardiac rupture through a calcified myocardial infarct after the formation of a myocardial aneurysm. They suggested that this occurred as a result of the localization in the aneurysm of an inflammatory process secondary to bacteremia from a perinephric abscess. In one instance of rupture of a ventricular aneurysm, encountered by Yater and

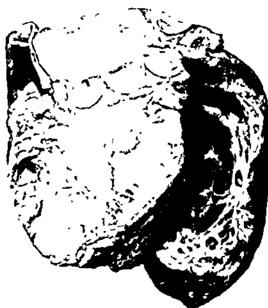


Figure VII-37. Multiple old healed infarcts. The wall of the aneurysm was the seat of calcification. (WCGH, 34 A 29)

associates (1948c), the aneurysm appeared to be the result of a fresh infarct. Rupture of a ventricular aneurysm may also be traumatic (Monckeberg, 1924).

Arteriosclerotic Aneurysm of Coronary Artery. A small proportion of aneurysms of the coronary arteries develop on the basis of atherosclerosis. In a review of the literature, Mitchell (1947) encountered 17 instances of atherosclerotic aneurysm In five of these, rupture and death ensued, in the others the finding was incidental For a discussion of aneurysm of coronary arteries from other causes, see page 634.

Prognosis

Survival after Onset of Angina Pectoris, Coronary Occlusion or Myocardial Infarction. *Survival depends on a number of* factors, including the nature and extent of the arterial disease, previous occurrence of infarcts, the severity of the attack, the presence of shock, the amount of muscle damage, and the development of arrhythmias, congestive failure or complications, particularly thrombosis and embolism

Coombs (1932) pointed out that the prognosis depends more on the severity of the attack than upon the state of the patient before the attack He believed the degree of reduction in pulse pressure to be the single most important sign; that a considerable fall in systolic pressure was significant, and that extreme pallor was an ominous sign. With the increasing recognition of milder forms of coronary occlusion and with improved methods of treatment, the mortality rate is diminishing. The vast majority of patients recover from the initial attack of occlusion This compares with earlier estimates by various authors of mortality rates averaging about 50 per cent. The prognosis becomes more serious with succeeding attacks

In their study of heart failure from coronary thrombosis, Master, Dack and Jaffe (1937) found a mortality rate of 4 per cent in the absence of failure and of 30 per cent in the presence of failure. In failure of the left ventricle alone the mortality rate was 4 per cent; in failure *of both ventricles, the rate was 40* per cent. The average age of those who died without evidence of cardiac failure was 49 years, of those with heart failure, 57 years. They found the following signs associated with heart failure and with a poor prognosis in acute coronary occlusion: pulse rate of 100 or more, pulse pressure of 20 mm. or less, muffled or "tic-tac" heart sounds, diastolic gallop rhythm, respiratory rate of 28 or more, cyanosis, orthopnea, pulmonary edema, fever above 101° F. and severe shock Arrhythmias were usually transient and did not alter the prognosis. (Accord*ing to Thompson and Levine [1936], the* prognosis is made worse by the occurrence of pulsus alternans, especially if it appears *within a number of hours or a few days* after the onset of acute infarction) Master and associates believe that hypertension, although an etiologic factor in coronary occlusion, apparently has little effect on the mortality rate The mortality rate rose from 11 per cent in the first attack to 50 per cent in the third attack.

Drake (1940) thought that the immediate mortality of coronary thrombosis under the best conditions is about 15 per cent. Drake quoted references to reported cases with survival of 18 years and 24 years and reported survival of a patient for nearly 40 years after an initial attack of myocardial infarction at the age of 40.

Master and associates (1943) found that when the systolic blood pressure fell below 80, the patient usually died, the height of the blood pressure did not significantly in*fluence the future course of the patient* with respect to subsequent angina pectoris, heart failure, coronary occlusion or death.

White and co-workers (1943) studied the duration of disease in 497 patients with angina pectoris. Of the 445 patients who

had died up to the time of their report, the average duration of the disease was 7.9 years. The average duration in the 52 persons who were still living was 18.4 years and it was estimated that the average duration for the entire group would be about 10 years.

Parker and associates (1946) made a follow-up study of 3440 patients with angina pectoris. The mortality rate for this entire group during the first year after diagnosis was 18 per cent, and approximately 10 per cent annually among survivors in each subsequent year. The rate was higher for men than for women, and for patients in the fourth decade than for those belonging to older decades. The rate was higher also in the presence of cardiac hypertrophy, hypertension, congestive heart failure, significant electrocardiographic abnormalities, and previous myocardial infarction. Smith and associates (1951) found that the mortality rate was not increased among their group of patients giving a history of antecedent angina

Chambers (1946) observed 100 consecutive patients (average age 59 years) in their initial attack of acute myocardial infarction Thirty-four died within one month and another eight within a year. Of the 58 who survived one year, nine had nonfatal recurrent infarctions. The average age of those who died was three years greater than that of the survivors. He (1947) found antecedent hypertension in 74 per cent of patients, but no relation between antecedent hypertension and the mortality rate. An early return of the blood pressure to normal or pre-occlusion hypertensive levels was found to be a good prognostic sign; in the fatal group the blood pressure did not return to its former level.

Master (1947) estimated the mortality rate from all cases of acute coronary occlusion to be less than 20 per cent, and for the first attack, to be less than 10 per cent.

Katz (1947) determined that about one-fifth of patients studied with recent myocardial infarction died during their hospital stay, and that the average expectancy of life following an infarct is five years. He found that some patients lived comfortably for over 20 years following an infarction. Patients whose blood pressure fell markedly and patients in shock had a poor prognosis. He stated that infarction is more benign than is generally appreciated; that it usually is self-limited; and that by the time the clinician sees the patient, the latter is already convalescing.

Yater and associates (1948c) determined that shock occurred in 17 per cent of their patients with coronary artery disease at the onset of the attack, and that it was eight times as common in men who died as in those who survived. As a rule younger patients lived longer; also, as a rule, the greater care the patient exercises following recovery from the effects of coronary occlusion, the longer will he live (White and Bland, 1931).

Katz and associates (1949) again studied the length of survival of 507 persons hospitalized for recent myocardial infarction They found that approximately one-fourth were dead at the end of two months, one-half at the end of one year, two-thirds at the end of the third year, and four-fifths at the end of five years. The group which had had heart failure or diabetes at the time of admission showed a greater mortality rate at the end of two months and for the entire period studied.

A rectal temperature above 104° F., a leukocyte count over 25,000 or a venous pressure over 200 mm. of water indicates a grave prognosis, according to Shillito and associates (1942). Seven of 8 of their patients showing any of these signs died within 16 days after the coronary attack. Although almost all of their patients showed an increase in the sedimentation rate, the degree of its increase was not

found to be a reliable index to prognosis. Goodrich and Smith (1936) believed that a count of nonfilamented polymorphonuclear leukocytes in excess of 30 per cent after the fourth day of an attack of coronary occlusion constituted an unfavorable sign. Smith and associates (1951) noted that a high leukocyte count indicated a worse prognosis In their series of 920 patients with acute myocardial infarction as determined by electrocardiographic evidence or autopsy, the mortality rate was 13 per cent among those having a leukocyte count of 10,000 to 15,000, 28 per cent among those with a count of 15,000 to 20,000, and 38 per cent among those with a count of over 20,000.

Smith and associates (1951) calculated that the mortality rate in their series of patients with acute infarcts was 42 per cent among those who developed thromboembolic complications as compared with 20 per cent among those who had no such complications. The therapeutic use of anticoagulants within recent years has significantly reduced the incidence of thrombosis and embolism following myocardial infarction and the mortality rate in this group of patients (Allen *et al.*, 1947, Wright *et al.*, 1948, Nichol and Borg, 1950, Smith *et al.*, 1951).

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Vascular Lesions of the Heart

B. Lesions Other than Coronary Sclerosis

Occlusive Lesions

Coronary Embolism. Most instances of coronary embolism are secondary to bacterial endocarditis of the left side of the heart The anterior *descending branch of* the left coronary is the artery most commonly involved Embolic occlusions of large coronary branches are usually single, emboli to small coronary branches are nearly always multiple. In order to diagnose embolism at autopsy, one should be able to determine the source of the embolus Absence of inflammation or of other lesion of the wall of the obstructed vessel at the site of the occluding material speaks in favor of the embolic nature of the occluding process. Hamman (1941) reviewed 30 cases in the literature of embolic occlusion of large branches and added 10 cases of his own. He estimates that from 1 to 2 per cent of cases of coronary occlusion are due to embolism and predicts that the incidence from this cause will be found to be greater with further study. He lists six possible sources of emboli of coronaries: (1) a thrombus or atheromatous material in a coronary artery, (2) a thrombus covering an atherosclerotic plaque at the root of the aorta, (3) a bacterial vegetation on the mitral or aortic valve, (4) an intracardiac mural thrombus, (5) a thrombus in a pulmonary vein; and (6) a thrombus in a peripheral vein (paradoxic embolism).

In the 40 collected cases, the source of embolism is not stated in 2; 2 belong to the first group, 6 to the second, 19 to the third, 5 to the fourth, 2 to the fifth, and 4 to the sixth All 6 cases in the second group occurred in men, 5 of whom were relatively young (24 to 35 years) In 4 of these five cases, the disease of the aorta upon which the thrombus formed was atherosclerosis; in one, syphilis. The two organs that suffer most from the effects of infarction are the brain and the heart; cerebral embolism is more common than coronary embolism

Saphir's (1933, Case 2) patient was a 70-year-old man with coronary sclerosis, thrombosis and myocardial infarction. The thrombus, present in the proximal portion of the circumflex branch of the right coronary artery, partially occluded the vessel. It was estimated to be six days old. A portion of the thrombus then broke off and lodged distally at the site of origin of the posterior descending branch. The embolism caused sudden death. T



Figure VII-38 Recent thrombosis of left circumflex artery with embolism into more distal portion of the vessel Fresh infarction and rupture of left ventricle (WCGH, 46 A 64)

illustrates the value of careful and complete dissection of the coronary arteries. Two similar cases involving men aged 47 and 49 were reported by Jaffé (1940). A similar instance of embolism, in which the patient died as a result of ventricular rupture, is illustrated in Figure VII-38.

Hadorn (1938) reported the occurrence of thrombotic occlusion of a coronary artery with resulting myocardial infarction and mural thrombosis; a portion of the mural thrombus broke off and lodged in the same coronary artery, causing sudden death of the patient. In pneumonia embolism is rare since thrombi do not ordinarily form in the pulmonary veins Thrombosis of the veins occurs only if there is suppuration of the veins or invasion by tumor.

Medlar (1935) reported plugging of a branch of the left coronary artery by a bit of caseous material containing tubercle bacilli. There was no evidence of previous disease of the artery. The patient had bilateral pulmonary tuberculosis, a small cavity in the upper lobe of the right lung and generalized miliary tuberculosis. In addition there was an area, measuring 3 x 1.5 cm., of recent infarction of the lateral and upper portion of the left ventricle, the infarct being judged to be a few days old. The patient died unexpectedly as the result of the embolism.

Moragues and associates (1950) reported the occurrence of embolism with survival for several months. The source of the embolus was a nodular calcified mass on the aortic valve which had no associated bacterial endocarditis.

The immediate prognosis of embolism of a coronary artery or one of its larger branches is poor, but if the patient survives the initial effects of the embolism the chances are good that the recovery will be complete. The diagnosis may be made during life if the patient has bacterial endocarditis or thrombophlebitis and develops symptoms of coronary occlusion. In bacterial endocarditis emboli commonly occlude small branches of the coronary arteries. De Navasquez (1939) examined serial sections of successive blocks cut from the left ventricular wall and septum in 20 unselected cases of *Streptococcus viridans* endocarditis He found evidence of embolism to small arteries in 19 of the 20 hearts. In 16, sharply defined masses were found within the lumen of an artery and in 19, foci of polymorphonuclear leukocytes, with or without necrosis of adjacent myocardial cells, were found in the myocardium. In no instance, however, were bacteria demonstrable in these lesions. Saphir (1935) found small organizing myocardial infarcts in 28 of 35 unselected cases of subacute bacterial endocarditis. These small emboli produce no symptoms unless they are nu-

merous, when they may seriously impair cardiac efficiency. Coronary embolism of bland thrombi is rare, of bacterial vegetations common

Paradoxic Coronary Embolism. Only a few cases of paradoxic or crossed coronary embolism have been reported. For paradoxic embolism to occur, it is necessary that a defect with patency of the atrial or ventricular septum be present and that the pressure in the right chamber exceed that in the left. An increase in pressure of the right side with development of acute cor pulmonale often follows massive or recurrent pulmonary infarction and may set the stage for crossed embolism. In this connection it must be remembered that probe-patency of the foramen ovale is found in from 20 to 25 per cent of all human hearts (see page 80). In all the following instances, a patent foramen ovale was present The patient (Case 11) of Wolff and White (1926) was a woman with carcinoma of the ovaries who had pelvic venous thrombosis and embolism which involved the patent foramen ovale and the descending branch of the left coronary artery The patient of Thompson and Evans (1930) had a malignant teratoma involving both testes. Portions of the neoplasm metastasized by way of the veins to the right side of the heart and were carried through the patent foramen ovale into the left ventricle and both coronary arteries In Saphir's (1933) Case 1, the embolus arose in a thrombosed femoral vein and lodged in the left anterior descending coronary artery Saphir attributed sudden death of the patient, aged 35, to lack of development of coronary anastomoses because of the young age of the patient and his freedom from coronary atherosclerosis A similar case in which the embolus arose in a femoral vein was reported by Jacobi and associates (1934).

Air Embolism of Coronary Artery. In experiments on guinea pigs, in which bronchovenous fistulas were produced with entrance of air into the pulmonary veins, Rukstinat and LeCount (1928) were able to demonstrate air in the coronary arteries in all animals. In fatal cases, death was abrupt, some animals showed focal microscopic hemorrhages in the myocardium, in other animals, no focal lesions were present Rukstinat (1931) injected air into the coronary arteries of dogs. When 15 to 20 ml was injected rapidly, death ensued within one to four minutes, but if the injection occupied 40 to 50 seconds, the cardiac disturbance was slight and the animal recovered

A number of instances of fatal air embolism (Lucas, 1936, Hall, 1937, Schattenberg and Ziskind, 1939) have occurred in refilling an old pneumothorax in which air has entered a pulmonary vein, and air emboli have been found in the cerebral vessels, and in the coronary arteries with or without hemorrhagic areas in the myocardium A similar accident may follow thoracentesis or thoracic operations (Helper *et al*, 1947)

Rossle (1947) believes that in fliers, and in victims of explosion in the air or under water, there are sudden changes in the atmospheric and intra-alveolar pressures, with rupture of the pulmonary capillaries and entrance of air into the pulmonary capillaries or veins, air thus reaching the left side of the heart and coronary arteries Air embolism to the brain may result in unconsciousness while air embolism to the coronary arteries may result in sudden death.

Durant and associates (1947, 1949) have reviewed the literature on air embolism They believe that most cases of serious "pleural shock" in reality represent air embolism. They distinguished between pulmonary (venous) air embolism and arterial air embolism, depending on the site of entrance of air In the pulmonary form, air enters one of the systemic veins and is

carried to the right side of the heart and pulmonary circulation In the arterial form, air enters a pulmonary vein and is carried to the left side of the heart and then to the systemic arteries In the pulmonary form, should the heart possess a patency of the interatrial septum, as of the foramen ovale, paradoxic air embolism may result

In pulmonary air embolism, death results from circulatory obstruction because of an air trap in the right ventricular outflow tract. The amount of air necessary to cause death is relatively large, being 150 ml or more. In arterial air embolism, a relatively small amount of air is necessary Involvement of the coronary arteries is believed to be a factor in causing death. Durant and associates (1949) demonstrated that the injection of 0 5 to 1 ml. of air into the coronary arteries of dogs, or of 5 to 10 ml of air into the left atrium or pulmonary veins produced ischemia of the myocardium in areas supplied by the involved vessels. The ischemia was also indicated by electrocardiogram and was demonstrable grossly Two dogs survived injection of 5 ml of air into the left atrium and two dogs died following injection of 10 ml of air. These workers found that the vascular obstruction may be transient, the air being rapidly absorbed, but that the ischemia may persist despite the disappearance of air bubbles from the lumen of the coronary arteries.

Fat Embolism. In fat embolism following trauma, Warthin (1913) called attention to possible damage to the heart. He pointed out the macroscopic presence of fat in subepicardial vessels, miliary hemorrhages and patches of fatty degeneration in the heart muscle; and in microscopic sections, fat-emboli in numerous blood vessels, and large droplets in the heart muscle in the immediate neighborhood of these vessels. Some of the fat in the muscle fibers apparently is derived from the neighboring fat-emboli. The fatty material is transferred from the venous to the arterial side by passing through the pulmonary capillaries. This transfer is said to be favored by subsequent trauma or jarring of the patient (Vance, 1931). The fat is distributed to the capillaries of the entire circulatory area but the principal effects of the embolism appear to be manifested in the brain, heart, kidneys and lungs. Plugging of the capillaries and arterioles results in focal anoxia and minute infarcts with petechial hemorrhages. In the heart the hemorrhages may be minute and in the form of streaks in the ventricular muscle, while the adjacent muscle may reveal numerous microscopic fatty globules.

Szurek and Czaja (1933) injected 1 to 2 ml. of oil obtained from canine adipose tissue into the descending branch of the coronary artery of dogs and exsanguinated the animals after various periods from 6 hours to 30 days. They found sausage-shaped fatty emboli causing occlusion of the capillaries. Some oil was still present after 30 days. Permanent blocking by oil was followed by focal infarction. In the pulmonary form of fat embolism, Warren (1946) gave the location of petechial hemorrhages as pericardium, conjunctivae and pleurae in that order of frequency. He stated that fat may pass the pulmonary circuit or go through a patent foramen ovale, but doubted that embolic involvement of the coronary arteries was a significant factor in producing death. In cases in which the coronaries were involved, other organs were severely affected. In 8 of 100 cases of fat embolism he found a significant degree of coronary involvement.

Harman and Ragaz (1950) produced fat embolism in rabbits by the intravenous injection of homologous fat. In animals dying immediately, death was ascribed to massive plugging of the pulmonary vessels. In animals that survived the injections by several hours, the principal changes were

pulmonary edema, focal necrosis in the heart and liver, and scattered petechiae The changes in the heart included petechial hemorrhages of the pericardium and beneath the endocardium of the left ventricle, and presence of grossly perceptible fat globules in the dilated right ventricle, and microscopically, hyperemia of the myocardium and focal necrosis with infiltration of monocytes and neutrophilic polymorphonuclear leukocytes. The focal necrosis was attributed to embolism of small vessels by fat.

Dissecting Aneurysm of Coronary Artery. Only a few instances of dissecting aneurysm of the coronary arteries have been reported.

Wainwright (1944) described an instance of dissecting aneurysm of the aorta which extended to produce dissection of the left coronary artery and its anterior descending branch and consequent occlusion of the lumen of the vessel by the pressure of the hematoma within its walls, and myocardial infarction. He believes that the rarity of obstruction of the coronary artery from this cause is to be explained by the proximity of the coronary orifices to the reflection of the pericardium on the aorta, rupture usually occurring into the pericardial sac before the dissection can extend widely in the walls of the coronary arteries The anatomic relations of the orifices in the sinus of Valsalva are also thought to afford protection against dissection of the coronary arterial walls.

Coronary Arteritis without Aneurysmal Formation. Barnett and Zimmerman (1947) reported an instance of thromboarteritis of the coronary artery in a 48-year-old man with septicemia caused by *Salmonella choleraesuis*. The renal and hepatic arteries were similarly involved. The sections were reviewed by Klemperer and the lesions were judged to represent those of true arteritis rather than manifestations of polyarteritis nodosa.

Compression of Coronary Artery by Neoplasm. Peppard and Larson (1933) reported occurrence of metastatic carcinoma from the breast to the epicardium with compression of lumen of both coronaries but especially the left. The myocardium was soft but not infarcted.

Obstruction of Coronary Sinus. Grant and Jones (1928) encountered at autopsy in a 28-year-old man a fibrous diaphragm which occluded the lumen of the coronary sinus in its mid-portion. The fibrous tissue appeared to be the result of an old thrombus of the sinus, rather than a congenital malformation. In this case it is of interest to note that the obstruction apparently caused no interference with coronary circulation and did not produce obvious dilatation of the tributary veins, thus indicating the functional efficiency of the venous anastomoses present on the surface of the heart

In experiments on dogs, Lorber and Greenberg (1944) demonstrated that gradual occlusion of the coronary sinus did not increase the coronary arterial bed but rather reduced it.

Warner and Dauphinee (1936) encountered complete occlusion of the coronary sinus by a thrombus in a 45-year-old man with widespread migratory phlebitis and carcinoma of the bronchus Clinically the patient had severe dyspnea and paroxysmal tachycardia, but no cardiac pain. The diagnosis of phlebitis with thrombosis was made during life after excision of a superficial vein

McAllister and Leighninger (1950) produced infarction of the right ventricle in dogs by ligating both the coronary sinus and the anterior cardiac veins, indicating that the intramural venous drainage system (thebesian vessels) was incapable of accommodating the inflow of oxygenated blood to this area.

Miscellaneous Lesions

Aneurysm of the Coronary Arteries. Scott (1948) reviewed the literature on aneurysms of the coronary arteries. He classified these aneurysms as localized, diffuse and dissecting. Of 47 localized aneurysms, 15 were regarded as congenital, 12, mycotic-embolic, 6, arteriosclerotic, 6, syphilitic, 1, purely mycotic, 1, rheumatic, 2 probably caused by periarteritis nodosa, and 4 unclassified The left coronary artery only was involved in 27 instances, the right artery only in 11, and both arteries in 6, and in 3 instances the affected artery was not named. In 36 instances a single aneurysm was present, in 8, multiple aneurysms; and in 3 instances no statement is made, but presumably a single aneurysm was present. Fourteen of the 15 instances of congenital aneurysm were encountered in males In the arteriosclerotic aneurysms the internal elastic layer may be destroyed at the site of atheromatous plaques The mycotic-embolic aneurysms are usually secondary to bacterial endocarditis of the mitral or aortic valve The commonest causes of death in the localized aneurysms were rupture (in about 50 per cent of cases), coronary thrombosis and congestive heart failure Scott reported the occurrence in a man of 84 of multiple aneurysms involving both coronaries, the largest aneurysm measuring 10 × 8 × 8 cm. A roentgenogram revealed a large globular shadow to the right of the heart and displacement of the esophagus to the left, while the electrocardiogram revealed a shifting pacemaker. The patient, however, had had no cardiac symptoms.

A single aneurysm of the coronary is usually situated immediately distal to the orifice, within the first inch of the vessel; multiple aneurysms are usually located at points of division of the artery (Packard and Wechsler, 1929). Scott also found 5 reports of diffuse aneurysm and one of dissecting aneurysm. All of the diffuse aneurysms were thought to be congenital; 4 of them involved the right coronary and one the left circumflex.

Fraenkel (1917) reported an instance of aneurysm of the left coronary artery immediately beyond the orifice. It was found in a 20-year-old soldier, who had sustained an injury to the right upper arm and head six months previously. The aneurysmal vessel was filled with a red thrombus and was associated with aneurysmal bulging of the apical half of the left ventricle and with a mural endocardial thrombosis. Fraenkel thought that a traumatic origin was likely.

In the mycotic-embolic aneurysms the lumen contains the infected embolic material. The infection first involves the intima and then spreads either directly to the media and adventitia or to the adventitia by way of the vasa vasorum and finally to the media. There is inflammatory reaction with infiltration of polymorphonuclear leukocytes and lymphocytes and destruction of the internal elastic lamina, fibroblastic proliferation, later destruction of muscular tissue and finally hemorrhage in the adventitia and surrounding tissue. Occlusion of the lumen of a coronary artery by embolus from vegetative endocarditis may cause myocardial infarction. Pure mycotic aneurysms are secondary to septicemia, as from osteomyelitis. In view of the great rarity of the so-called arteriosclerotic aneurysms, the arteriosclerotic process may be but one factor in the production of these aneurysms. In addition to the severe atherosclerosis, the vessel at the site of an atheromatous plaque may have undergone destruction of the internal elastic lamina and atrophy of the media.

Anoxic Necrosis of Coronary Arteries in the Newborn. Gruenwald (1949) encountered necrosis in the media of the coronary

arteries of stillborn and newborn infants in 21 subjects or in 9 5 per cent of subjects up to three days of age who showed signs of asphyxia, including focal hemorrhages in various organs. The areas of necrosis consisted of masses of eosinophilic material, chiefly in the outer portion of the media, which were focal or surrounded most or all of the vessel. Some of these lesions enclosed cavities containing granular debris and occasional erythrocytes. The lesion appeared to progress from the adventitia toward the intima and suggested impairment of the nutrition of the vessel wall, derived from the adventitia.

Rupture of Coronary Artery. Olcott (1931) reported a case of rupture of a coronary artery and found 30 cases in the literature. Fifteen of the 31 cases were associated with coronary aneurysm, and 16 were not. In 14 the etiology was thought to be atherosclerosis, in 5 an infection (embolic), in 2 syphilis, and in 10 undetermined. The average age of the patients of the infectious group was 19 years, of the syphilitic group, 46, and of the arteriosclerotic group, 65 The vessels involved and the frequency of involvement were as follows left coronary artery 11 times, the right 8, both vessels 3 and in 9 instances the vessel affected was not stated The subjects were males in 19 cases, females in 11, and in one instance the sex was not stated Bradbury (1942) reported survival of a woman (aged 75, alive and comfortable at the time of the report) for 32 years following severance, by a stab wound, and ligation of the mid-portion of the anterior descending branch of the left coronary artery.

Coronary Arteriovenous Fistula. Paul and associates (1949) reported 2 instances of congenital coronary arteriovenous fistula encountered on exploratory thoracotomy, one in a 9-year-old boy and one in a 16-year-old boy In neither case was surgical treatment of the condition attempted. The 16-year-old subject had a patent ductus arteriosus complicated by streptococcal bacterial endocarditis, the latter infection was successfully treated with penicillin. Halpert (1930) reported an incidental finding, at autopsy of a 54-year-old man who died of cancer of the stomach, of a congenital arteriovenous communication between a greatly dilated and tortuous right coronary artery and a dilated coronary sinus. There were no other congenital cardiac anomalies and the patient had no obvious cardiac disturbance during life.

Varices of the Heart. A common site for varices of the coronary system is the right atrium at the inferior or posterior border of the foramen ovale (Schulz, 1930) Other sites include papillary muscles, a leaflet of the tricuspid valve and the subepicardial fat. Varices are formed on the basis of a congenital underdevelopment of the venous wall. The lower pressure within the right atrial chamber may also be a factor in their formation. In most instances, varices have been encountered in aged persons and have had no clinical significance

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Rheumatic Disease of the Heart

ARCHIE H. BAGGENSTOSS

Historical

According to Wells (1812), Pitcairn, about the year 1788, first remarked that persons subject to rheumatism were "attached more frequently than others, with symptoms of an organic disease of the heart." Subsequent experience confirmed the truth of this observation and he concluded that these two diseases often depended on a common cause, and called the latter disease "rheumatism of the heart." He communicated his observation to several of his friends, and to his pupils at St. Bartholomew's Hospital, to which he was then physician, but no notice was taken of his remark in any book before it appeared in the second edition of Baillie's *Morbid Anatomy*, published in 1797.

Jenner was also among the first to associate rheumatic fever with heart disease. According to records of the Fleece Medical Society, of which Jenner was a member, on July 29, 1789, "Mr. Edward Jenner fa-

vored the society with remarks on a disease of the heart following acute rheumatism illustrated by dissections." A classic account of the association of acute articular rheumatism and heart disease was written by Jean Bouillaud in 1835 In his famous law of coincidence, he stated (1840): "In the great majority of cases of diffuse articular rheumatism with fever there exists in a variable degree a rheumatism of the serofibrous tissue of the heart The coincidence is the rule, and the noncoincidence the exception."

Baillie in 1793 first described the acute form of pericarditis with exudation of "coagulable lymph" from the blood vessels in the pericardium and fluid in the pericardial cavity Pulteney in 1761 had reported a case of adherent pericardium in a young man who had suffered from fever and arthritis two years previously

In 1835 Sir Thomas Watson recognized rheumatic fever as essentially a disease of childhood "One law respecting the connection between the cardiac and the arthritis symptoms may be stated with confidence, namely, that the younger the patient is who suffers acute rheumatism (and I have seen it as early as the third or fourth year) the more likely will he be to have rheumatic carditis. The chance of this combination appears to diminish after puberty as life advances"

MacLagan in 1881 emphasized the specific action of the salicylic group of drugs. Salicylic acid was the first of these to be used in the treatment of acute arthritis but because of its irritant action it was supplanted by sodium salicylate. Cheadle (1889), in his lectures before the Harveian Society of London in 1888, presented a classical description of rheumatism in childhood to which little can be added at the present time.

It was not until the latter part of the nineteenth century that rheumatic myocarditis was recognized The myocardial lesions were described by several investigators (Goodhart, 1879; Romberg, 1894) before the specificity of the interstitial myocardial lesion was established by Aschoff in 1905.

In 1887 the microbic origin of rheumatic fever was investigated by Mantle. In the next twenty years the names of Geipel (1905), Poynton (1899) and Paine (1900), and Coombs (1907) were associated with further discussion of the pathology and etiology of rheumatic disease. In the past 35 years, investigators have been engaged in bacteriologic and immunologic studies in unsuccessful efforts to determine the etiologic agent of the disease. The majority of these studies have centered about the possible etiologic significance of microorganisms of the genus Streptococcus.

The main contribution to our knowledge of rheumatic fever during the past twenty years has been in the field of pathology. The studies of Klotz (1912), Pappenheimer and Von Glahn (1924, 1927), MacCallum (1924), Klinge (1933), Swift (1924, 1929, 1947), Gross (1935a, b), Clawson (1925, 1929, 1938, 1940a, b, 1941, 1945), and others clearly demonstrate that rheumatic fever is a systemic disease, probably an infection producing lesions throughout the body. Most important of these is the lesion of the cardiovascular structures

Prevalence

Rheumatic disease of the heart ranks with coronary and hypertensive heart disease as one of the most common and serious types of disease of the heart It is especially important and serious because it is particularly a disease of youth, crippling and killing many children and young adults. The statistics collected by Paul (1928, 1934, 1945) from surveys of school children of some of the large cities of the United States indicate an incidence of rheumatic heart disease of approxima

three to 14 cases per 1000. Glover (1930) in England found that in the age group 10 to 15 years, rheumatic fever causes 5.4 per cent of all deaths and heart disease (80 per cent of which was due to rheumatic fever at this age), 10.8 per cent or a total of 16.2 per cent. This is four-fifths as much as all forms of tuberculosis and more than twice as much as measles, scarlet fever and diphtheria combined. In the United States rheumatic fever with heart disease is the leading cause of death during the age period from 10 to 15 years. At ages 15 to 24 years it is second only to tuberculosis. It has been estimated that, among persons less than 20 years of age, for each death due to the combined causes of pertussis, diphtheria and poliomyelitis there are 50 deaths due to rheumatic disease of the heart (Mustard, 1947).

Natural History

It is now generally recognized that rheumatic fever is a chronic inflammatory disease. Cohn and Lingg (1943), in a statistical study of 3129 patients, noted recurrences in 75 per cent during an average period of 13 years after the onset of the illness The largest incidence of recurrence was in patients between the ages of five and 14 years According to these authors, a sharp decline in recurrences takes place at the age of 12 years, involvement of the heart can be recognized in approximately 65 per cent of patients during the course of rheumatic fever in childhood; and the earlier the age at onset, the greater is the chance that infection will be severe during the next few years.

In a ten-year study of 1000 cases of rheumatic fever, Jones and Bland (1942) found that 65.8 per cent had some degree of rheumatic heart disease while 34.2 per cent had no detectable heart disease at the termination of their first attack. In this latter group of 342 patients, about 72 per cent were free of rheumatic heart disease at the end of 10 years whereas 27 per cent had rheumatic heart disease. Two-thirds of those who later had rheumatic heart disease had a recognizable recurrent episode of rheumatic fever whereas in one-third the recurrence of the disease was so mild that it was unrecognized. Of the 658 patients who had rheumatic heart disease at the end of their initial attack of rheumatic fever, the cardiac condition of 22 per cent improved, that of 27 per cent was unchanged and that of 51 per cent had progressed at the end of 10 years. The development or absence of recurrent rheumatic fever was the chief feature which determined whether rheumatic heart disease would progress or regress. In 75 (7.5 per cent of the entire series) clinical evidence of rheumatic heart disease disappeared while in 68 (6.8 per cent of the total series) it decreased. At the end of ten years the status of the heart disease in these 1000 patients was as follows: 313 (31.3 per cent) had no detectable heart disease; 470 (47 per cent) had some degree of rheumatic heart disease; 203 (20.3 per cent) were dead, most of them as the result of recurrent rheumatic fever; and concerning 14 (1.4 per cent) the follow-up data were too inadequate to be of value. Six hundred and forty-eight were able to lead normal lives 16 years after the onset of rheumatic fever. This number included 313 without detectable heart disease, 209 with slight rheumatic heart disease, and 126 whose only restriction was avoidance of competitive exercise and severe physical strain.

According to Cohn and Lingg (1943), the duration or life expectancy differs with the age at onset. When the disease begins in childhood, 69 per cent survive childhood, 35 per cent survive adolescence, 18 per cent reach the age of 30 years and 5 per cent live beyond the age of 45 years. When the disease begins in adolescence, 85 per cent survive this age period, 55 per

cent reach the age of 30, and 21 per cent the age of 46 or more. When the onset is in the third decade, 23 per cent survive the age of 45 years; and when the onset is after 30, 44 per cent survive the age 45.

Somewhat similar findings have been reported by Ash (1948) in a study of 537 children in Philadelphia observed for 10 years after the onset of rheumatic infection. At termination of the initial attack 59 2 per cent showed evidence of the presence of rheumatic heart disease. Of 219 patients with no clinical evidence of heart disease at termination of their first attack, 76 7 per cent still showed no evidence of heart disease 10 years after onset. Only 5 per cent of this group who did not have heart disease clinically, at the termination of their first attack had died of rheumatic infection or bacterial endocarditis. Of 318 patients who had rheumatic heart disease after the initial episode of rheumatic fever, 30 (9.4 per cent) showed disappearance of signs of cardiac involvement and 42 1 per cent had died of rheumatic infection or bacterial endocarditis. Of the group who had heart disease after the initial episode of rheumatic fever, 60 3 per cent of those living ten years after the attack were leading a normal existence with little or no limitation of activity. In the whole group also the majority of subjects presenting no functional incapacity at the end of ten years had not shown any clinical evidence of heart disease at the termination of the initial attack Also 24.4 per cent of the total group had died of rheumatic infection in comparison with a death rate of 42 per cent among those diagnosed as having rheumatic heart disease at onset.

Wilson and Lubschez (1948) reviewed the records of 1042 children who were under observation for a period of 30 years Eighty-nine per cent of the patients were seen at the time of death or at the end of the study The over-all death rate was 14 7 per thousand per year. The highest death rates occurred between the ages of one and four years (33 2 per thousand) and 10 to 14 years (16.3 per thousand). An affected child has four chances out of five to survive 15 years after the onset of the disease, three chances out of four to survive 20 years after onset and two chances out of three to survive 30 years after onset.

Cause of Death in Rheumatic Fever. In the study by Jones and Bland (1942) of 1000 patients with rheumatic fever, ten years after the initial attack one-fifth (203) had died, most of them (83 per cent) after *repeated episodes of rheumatic fever. Sixteen* (8 per cent) of the deaths were due to bacterial endocarditis superimposed on the previous rheumatic valvular disease. Nineteen persons died as the result of diseases or accidents unrelated to rheumatic fever or rheumatic heart disease. Among 226 deaths analyzed by Wilson and Lubschez (1948), 75 per cent were due to *rheumatic disease of the heart and 10 per* cent to subacute bacterial endocarditis. In the study of the first 10 years of rheumatic infection in 588 children, Ash (1948) found that one-fourth (131) had died from rheumatic infection, 2 per cent (12) from bacterial endocarditis and 1.4 per cent (8) from unknown or unrelated causes. On rare occasions sudden death occurs as a result of rheumatic carditis (Hamilton *et al.*, 1948, Moritz, 1948).

Etiology

PREDISPOSING CAUSES

Age. Rheumatic fever may begin at any age but it usually begins in childhood, especially between the ages of four and 10 years. In a study of 1042 children Wilson and Lubschez (1948) found that the mean age at onset was 6 5 years. The disease was observed in the great majority of cases between the ages of four and 50 years and rarely did it begin before the age of two years. An example of intra-uterine rheu-

matic heart disease was reported by Kissane and Koons (1933); Schwarz (1932) reported rheumatic heart disease in an infant aged 17 months. Of all instances of rheumatic cardiac disease two-thirds are found to begin in childhood. In the remaining third, the disease is acquired at later age periods. Over one-half (56 per cent) occur in adolescence. This group includes the survivors from childhood plus those who have acquired the disease in this age period Only 16 per cent were 45 years or older, and only 3 per cent were first affected after the age of 45 (Cohn and Lingg, 1943). The fact that the first attack of rheumatic fever may occur relatively late in life has been emphasized by Ferris and Myers (1935) who reported six cases in which the first attack occurred after the age of 60 years The course of the disease is similar to that in younger persons except that the manifestations in the joints are possibly less intense and more persistent. Rogers and Robbins (1947) pointed out that the initial as well as recurrent attacks of rheumatic fever in the later years of life may arise in the complete absence of characteristic clinical signs, progressing insidiously into acute cardiac decompensation and death

Although rheumatic fever usually begins in childhood, it should be emphasized that most rheumatic cardiac lesions are observed at necropsy in the older age groups. Most, but not all, of these lesions in older persons are quiescent or healed. In a chronic disease hospital, Kaufman and Poliakoff (1950) found 50 instances of rheumatic heart disease among 263 consecutive necropsies Twenty-eight per cent of the group with rheumatic heart disease were between the ages of 40 and 50, and 72 per cent between 50 and 81 years. In 16 of the 50 cases (32 per cent) clinical activity of the disease was found, while the subjects were on the wards, and evidence of this activity was found at necropsy. These figures indicate that heart disease of rheumatic type is quite frequent in old age.

Sex. In various reported series there is a slightly higher incidence of the disease among girls than among boys. In a series of 696 subjects reported by Wilson (1940), there were 387 girls and 309 boys, which is not a significant difference.

Climate. Rheumatic fever is especially prevalent in the temperate zones, is less frequent in the subtropics and is rarely seen in the West Indies (Swift, 1924, 1929, 1947) In Boston at the Peter Bent Brigham Hospital the incidence of rheumatic fever in the years 1914 to 1923 was 1.85 per cent of all medical admissions, the clinical incidence of mitral stenosis was 3.89 per cent, and the incidence of stenosis of the mitral orifice at necropsy was 4 68 per cent, while in New Orleans at the Charity Hospital those percentages from 1916 to 1923 were 0.03, 0.08 and 0 23, respectively (White, 1944). According to Clarke (1930), there is about 15 times as much rheumatic fever in the temperate climates as in the tropics. Bungeler (1942), however, stated that rheumatic fever is just as frequent in the tropics as elsewhere. Involvement of the joints is said to be relatively mild in the southern part of the United States whereas carditis may be severe. The incidence of carditis in the South, however, parallels the decreased incidence of rheumatic fever (Nichol, 1936). Classic polyarthritic manifestations are said to be rare in the central states whereas mitral stenosis is common These observations indicate a climatic influence on both incidence and clinical manifestations (Swift, 1924, 1929, 1947). Jones and his associates (1937) advised caution, however, with regard to the unquestionable value of transportation of patients with rheumatic fever to a subtropical climate.

Seasonal Incidence. Rheumatic fever is

usually prevalent in localities subject to cold and rain and to sudden wide fluctuations of temperature, irrespective of geographic location. In this country recurrences are more frequent in winter and spring than in the summer and fall.

Economic and Social Factors. It is generally thought that rheumatic fever is more common among the poor although its occurrence in the higher economic levels of society is not infrequent. Coburn (1931) found a ratio of 20·1 in New York City. In New Haven, Connecticut, Paul and associates (1934) found that 5 per cent of the school children in a poorer section of the city had rheumatic heart disease. This was one and one-half times the incidence of the disease in a public school in a better section of the city, and eight times that in a neighboring private school. Wilson and her associate (1948), however, found that the majority of the children with rheumatic fever surveyed in New York City came from moderately well-to-do homes of the industrial laboring class of the city. The British Medical Research Council (1927) did not find the economic factor to be of prime importance in the occurrence of the disease.

Nutrition. A number of studies have suggested that poor nutrition is a more important factor predisposing to the development of rheumatic fever than economic status. Vitamin C deficiency (Rinehart, 1935), high carbohydrate and low protein diets (Weston, 1948) have been considered important. It also has been demonstrated that giving patients a nutritious diet tends to prevent recurrences (Coburn and Moore, 1943)

Familial Epidemiology. Wilson's (1940) observation revealed a significantly greater prevalence of rheumatic fever among families in which parents had had rheumatic fever than among families in the same environmental group in which the parents had not had it. The data obtained by her study do not support the view that rheumatic activity is passed from one member to another member in the family. On the basis of genetic analysis, hereditary susceptibility underlies the familial incidence of the disease, although it probably is not the sole condition essential for its development. Aside from its occurrence in families, epidemics of rheumatic fever have been recorded in dwellings occupied by more than one family, and in military camps, schools and communities (Paul, 1945).

EXCITING CAUSES

Acute rheumatic fever has long been considered by many authorities to be an infectious disease. The etiologic agent responsible for the disease has been a subject of much controversy for many years.

Virus. Supportive evidence that a filtrable virus is the etiologic agent of rheumatic fever was presented by Schlesinger, Signy and Amies in 1935. They were able to obtain elementary bodies from the pleural and pericardial exudates of rheumatic fever patients by centrifugation at high speed. These elementary bodies were agglutinated only by the serum of patients who had active rheumatic fever. Eagles and associates (1937) also obtained suspensions of particles similar to the elementary bodies of virus infections from a variety of materials from patients who had acute rheumatic fever, rheumatoid arthritis and chorea. Suspensions of these particles were agglutinated by the sera of patients who had the particular disease affecting the patient from whom the material for the suspension was obtained. Control suspensions were not agglutinated by any of the rheumatic sera They were not able to produce rheumatic lesions by inoculation of the virus-like bodies into monkeys.

Bacteria. Poynton and Paine (1913) isolated a small diplococcus from the heart's

blood and other tissues in 8 cases of rheumatic fever in 1900 More recently the view that rheumatic fever is a manifestation of streptococcic infection has been gaining ground. Some investigators have held that it is due to a specific strain of streptococci (anhemolytic, Birkhaug, 1928; *Streptococcus cardio-arthritidis*, Small, 1927). Zinsser (1931) and, at one time, Swift (1924) asserted that a variety of different strains of nonhemolytic streptococci were responsible. Clawson (1925) and Cecil, Nicholls and Stainsby (1929) used special technics and obtained a relatively high percentage of positive cultures from rheumatic individuals. Clawson found streptococci in more than 50 per cent of cases of acute rheumatic fever but large amounts of blood had to be used and the organisms rarely grew in less than five days The organisms did not belong to a specific group but produced a green color and had rather low virulence. Clawson (1938) and other workers have succeeded in producing subcutaneous nodules similar to those of rheumatic fever by the inoculation of animals with streptococci. Dawson (1943), Nye and Waxelbaum (1930), and others either did not confirm these findings or discounted their significance

The study of Lichtman and Gross (1932) of 5283 consecutive blood cultures revealed that the incidence of recovery of nonhemolytic streptococci ranged from 4.0 to 15.5 per cent, with an average of about 6.0 per cent, in the following diseases: acute rheumatic fever with polyarthritis, chronic rheumatic heart disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, leukemia, colitis, meningococcic meningitis, pyelitis, and pyelonephritis. Callow (1933) isolated green-producing streptococci and pleomorphic bacilli with equal frequency from the blood of patients with rheumatic fever and from the blood of patients with nonrheumatic diseases. Wilson (1940) found that 46 per cent of 67 children of the rheumatic series and 41 per cent of 91 children in the control series had bacteremia. At present a majority of investigators seem to consider that organisms recovered from the blood of patients who have rheumatic fever are not of etiologic significance and probably represent transitory bacteremia.

The observations of Coburn (1931) have centered interest on hemolytic streptococci as one of the responsible agents for rheumatic fever. The concept that hemolytic streptococci are related in some undefined manner to rheumatic fever is now accepted by many investigators in this field. The following facts have been listed by Spink (1948) as evidence in favor of this hypothesis: 1. Upper respiratory infections due to group A hemolytic streptococci are frequently closely followed by rheumatic fever. In fact, epidemics of rheumatic fever have been associated with large numbers of cases of streptococcic respiratory disease. 2. Recurrent attacks of rheumatic fever are often preceded by streptococcic respiratory infections. 3. Patients who have active rheumatic fever reflect certain immune responses characteristic of invasion of the tissues by hemolytic streptococci such as an increased titer in the serum of antistreptolysin, antifibrinolysin and anti-M precipitins. 4. Although the sulfonamides do not alter the course of rheumatic fever, carefully controlled studies indicate that the prophylactic use of these compounds will prevent the invasion of tissues by hemolytic streptococci and thereby reduce the incidence of recurrent attacks of rheumatic fever.

Evidence contrary to the widely accepted view, that infection with hemolytic streptococci is responsible for the genesis of rheumatic fever, has been collected by Wilson whose studies indicate that the majority of recurrences in rheumatic children under observation were manifest in

the absence of accepted bacteriologic and immunologic evidence of preceding streptococcic respiratory infection. Although most of the children suffered from repeated respiratory infections, rheumatic fever followed such episodes only infrequently. According to Wilson, little evidence has been presented to date in support of the hypothesis that respiratory infection due to hemolytic streptococci is responsible for the initial attack of rheumatic fever. Investigations have been concerned mainly with the relationship of such infections to recurrences of rheumatic fever.

Hormones. Selye in 1946 was able to produce vascular lesions identical with those in periarteritis nodosa and hypertension, lesions like those of nephrosclerosis, and sometimes of acute nephritis and myocardial and articular lesions similar to those observed in acute rheumatic fever, by giving large doses of desoxycorticosterone acetate or anterior pituitary extracts. He postulated that the diseases of man which are thus imitated by overdosage of the hormone might arise as a result of an excessive production of endogenous salt-active corticoids. In this sense, these lesions would have to be interpreted as diseases of adaptation. In support of this concept he pointed out that fatigue, chills, traumatic injuries and mental upset may cause the relapse of rheumatic fever from a quiescent to an acute febrile state. It is interesting in this connection that Hench and his co-workers (1949) have found that certain clinical, biochemical and electrocardiographic features of rheumatoid arthritis and rheumatic fever have been improved by the daily intramuscular injection of either the adrenal cortical hormone, 17-hydroxy-11-dehydrocorticosterone (compound E) or the pituitary adrenocorticotropic hormone (ACTH). This may indicate that a lack of certain hormones rather than their overproduction is a causative factor in these diseases.

PATHOGENESIS

The question as to how any etiologic agent produces the morphologic and clinical picture of rheumatic fever has received considerable attention. Currently the disease is considered to be an allergic response of tissues previously sensitized by a specific or a nonspecific streptococcic infection. This hypothesis was suggested by Menzer (1902). Later it was re-introduced by Herry (1914) and received support from the experimental work of Faber (1915), Swift (1924, 1928, 1929, 1947), Zinsser (1931), Klinge (1931), Vaubel (1932), and Junghans (1934) Gross, Loewe and Eliasoph in 1929 and Bruun in 1940 repeated these experiments with only equivocal results and concluded that they had not reproduced a true analogue of the Aschoff nodule. More recently Rich and Gregory (1943) have been able to reproduce more closely the five supposedly pathognomonic features of acute rheumatic carditis. These have been listed as focal alterations of collagen, Aschoff nodules, focal and diffuse inflammatory lesions, focal alterations in cardiac muscle and valvular verrucae. In animals alteration of connective tissue was prominent in the endocardium near the valvular attachments and nodules developed about the foci of damaged collagen. Perivascular inflammation was frequent but formation of nodules in the adventitia of the arteries was not observed. No actual verrucae with thrombi were noted although the nodules frequently projected above the surface of the valve to give it a slightly warty appearance. As Mallory (1947) stated, the parallelism traced between the experimental lesions and the histologic findings in acute rheumatic fever is impressive if not complete. The observations of Rich and Gregory have been confirmed by Fox and Jones (1944) and McKeown (1947) but not by More and McLean (1949). Kyser,

McCarter and Stengle (1947) also have produced a similar type of myocarditis in rabbits with horse serum and have made the additional significant observation that antihistaminic drugs, such as diphenhydramine (Benadryl), will impede the development of the lesions.

Cavelti in 1947 found that rats immunized with combinations of killed streptococci and rat heart or connective tissue formed auto-antibodies to these tissues, demonstrable *in vitro,* and that the animals, apparently as a result of the pathogenic action of these antibodies, developed changes affecting chiefly the valves and the other connective tissue structures of the heart which resembled those of rheumatic fever. His hypothesis of the genesis of rheumatic fever is as follows: During or succeeding the streptococcic infection which precedes a rheumatic attack by about two to three weeks, an autogenous antigen is formed by a reaction in which streptococcic substances or their products combine with components of tissues, perhaps of connective tissue of the host. This antigen incites formation of specific antibodies which in turn precipitate the rheumatic lesions by reacting *in vivo* with the antigen situated in the tissues.

Clawson in 1945 was unable to produce endocarditis in rats by the injection of foreign proteins but was able to produce valvular lesions closely resembling acute rheumatic endocarditis in a high percentage of rats by injecting either green-producing or hemolytic streptococci into the blood stream. Lesions similar to those of bacterial endocarditis of human beings were produced on the same valve or on other valves in association with the rheumatic-like vegetations.

It is fairly obvious from a review of the conflicting experimental data that no final conclusion as to the etiology and pathogenesis of rheumatic fever can yet be made. The evidence indicating that the lesions of rheumatic fever are the result of a hypersensitive reaction (anaphylactic hypersensitivity, Rich and Gregory) is impressive but, as Mallory pointed out, the usual stigmata of allergy are lacking in cases of clinical rheumatic fever and direct proof of anaphylactic sensitization in the human being has yet to be advanced.

The significance of hyaluronic acid and hyaluronidase in the pathogenesis of rheumatic fever awaits the accumulation of further experimental studies (*J.A.M.A*, 1949). A possible relationship between hyaluronic acid, hyaluronidase and rheumatic fever is suggested by: (1) the proposal of Klinge that rheumatic diseases are primarily diseases of the cement substance, (2) the fact that sulfonamide compounds, admittedly inactive in rheumatic diseases, have no influence on hyaluronidase (Guerra, 1946); (3) the relatively low quantities (one-sixth to one-half of normal) of plasma enzymes with anti-invasive reactivity in patients with rheumatic fever as compared with healthy persons (Haas, 1946), (4) the inhibitory action of small amounts of sodium salicylate on the spreading of India ink or dye injected together with hyaluronidase (Guerra, 1946, Meyer, 1947); (5) Quinn (1948) and Harris and Harris (1949) have reported that the mean titer of an antibody to streptococcal hyaluronidase (spreading factor) was significantly higher in sera of patients with rheumatic fever than in sera obtained from convalescents of streptococcal or other infections, or from normal persons. Harris and Harris made the additional statement that the titer of antihyaluronidase in the sera correlated well with the activity of the rheumatic fever process; and (6) in 1944 Crowley observed that Types 4 and 22 were the only strains of Group A streptococci which did not contain hyaluronic acid, but did produce hyaluronidase. A report from the Committee on Rheumatic Fever (January,

1950) includes a statement that there were no reported instances of rheumatic fever following infection with Types 4 or 22, Group A streptococci Thus it appears likely that rheumatic fever occurs subsequent to an infection with those strains of Group A streptococci which contain hyaluronic acid.

Guerra is of the opinion that rapid extension of the involvement of mesenchymal tissue in rheumatic fever suggests a partial removal of the protective barrier (hyaluronic acid?) offered by the tissue ground-substance. Hyaluronidase is one of the substances capable of overcoming this barrier, although other enzyme systems may also be involved.

Lack of specificity of the relationship between hyaluronidase and rheumatic diseases is suggested by evidence that. (1) the inactivation of hyaluronidase by human serum is a complex reaction, the details of which are not yet completely understood. (2) the presence of inorganic ions such as chloride and phosphate may be as important as the relative concentrations of hyaluronidase and serum in patients with rheumatic disease (Meyer and Ragan, 1948), (3) changes in chondroitin sulfates and their protein complexes may be of greater importance for the rheumatic processes than the changes associated with hyaluronic acid (Meyer and Ragan); (4) Epstein and co-workers (1949) have reported that patients with active rheumatic fever did not have higher anti-hyaluronidase titers than did children with inactive rheumatic fever or those following streptococcal infection, but it was noted that these workers used bovine hyaluronidase as their test substance instead of the streptococcal hyaluronidase employed by Quinn, and by Harris and Harris, and (5) oral administration of salicylates affects the hyaluronic acid in synovial fluid, but it is unlikely that inhibition of hyaluronidase is the only (or even the most significant) *modus operandi* for the known antirheumatic effects of salicylates.

The evidence of a relationship between inactivation of hyaluronidase by human serum and the rheumatic diseases furnishes an interesting theory to explain the action of salicylates in rheumatic fever. However, at the present time the evidence must be considered more tentative than conclusive

MYOCARDITIS

Any discussion of rheumatic heart disease may well begin with the myocardium for three reasons First of all, as White (1944) so well stated, "The myocardium is the most important part of the heart If it is sound, a great deal of disease of endocardium and pericardium and great vessels, of valvular deformities and septal defects, and of strain from hypertension can be endured for a surprising number of years, if it is seriously diseased or fails, death may come quickly even though all the rest of the cardiovascular system is perfect." Secondly, the myocardial lesion is the foundation of our knowledge concerning the rheumatic injury The modern study of the histopathology of rheumatic fever began with Aschoff's description (1905) of the rheumatic nodule and his recognition that the nodule was the characteristic lesion of this disease If one recognizes and fully understands the rheumatic nodule of the myocardium, he will understand better the various other histologic manifestations of rheumatic fever Finally, the diagnosis of myocarditis is one of the most difficult for the clinician to make. As Saphir pointed out in 1941, "The incidence of the diagnosis of myocarditis has undergone more changes than perhaps the



Figure VIII-1 Hypertrophy and dilatation of left ventricle in acute rheumatic fever Patient was a boy 14 years of age The heart weighed 382 Gm (estimated normal weight, 216 Gm) Note verrucae on the mitral valve

incidence of any other diagnosis. Not so many years ago almost every elderly patient who died had 'chronic myocarditis' written on his death certificate." Now the term is in large part abandoned. Such wide swings in the medical pendulum indicate the lack of knowledge and the intrinsic diagnostic difficulties of the condition. If any improvement is to be made in this field of medical practice, it may well begin with a sound knowledge of the morphologic basis of the disease

The gross appearance of the myocardium of patients dying of active rheumatic fever may reveal little that is abnormal. Enlargement of the heart is usually present and produces a globular appearance On opening the chambers the enlargement is observed to be the result of hypertrophy and dilatation of the ventricles, particularly of the left ventricle (Figure VIII-1). This is true even in those cases in which there is no mechanical embarrassment such as valvular deformities or pericardial adhesions to explain the hypertrophy. The thickening of the ventricular wall is associated with thickening and lengthening of the papillary muscles and the dilatation of the ventricles is associated with dilatation of the atrioventricular rings. The latter may be so extensive as to give rise to slight degrees of insufficiency or incompetence. The gross abnormalities of the heart associated with various valvular deformities will be discussed for each valve separately.

The microscopic appearance of the reaction of the myocardium to rheumatic injury is most pronounced in the connective tissues of the heart, but evidence of direct injury to the myocardial fibers also is sometimes observed. For the sake of clarity the histologic appearance will be discussed in four divisions: (1) focal interstitial myocarditis (the rheumatic nodule); (2) diffuse interstitial myocarditis; (3) direct injury to the muscle fibers; and (4) lesions of the conduction system.

Focal Interstitial Myocarditis: The Rheumatic Nodule (Aschoff Body)

Since Aschoff's classic account (1905) of the rheumatic nodule, his assertion that the lesion is specific for rheumatic fever has received wide acceptance. It is also now generally recognized that as in tuberculosis so in rheumatic fever, there is one fundamental lesion with characteristics that may vary with the anatomic site and stage of development but which nevertheless represents the essential reaction of the tissues to the rheumatic injury. Because of this it is perhaps wise to start this discussion of the cardiac lesions in rheumatic fever with a fairly thorough description of the rheumatic nodule.

Although the histologic characteristics of rheumatic cardiac injury have been studied intensely and frequently described since Aschoff's report in 1905, attention except for a few noteworthy exceptions (Geipel, 1905, Thorel, 1910; Pappenheimer and Von Glahn, 1924, 1927; and Talalajew, 1929) has been concentrated primarily on the proliferative and exudative phases

of the inflammatory reaction to the neglect of what is now widely accepted as the primary injury to the connective tissue. The lack of study of this phase of the inflammatory process is understandable because it is relatively poorly developed in the myocardial lesions and often obscured by the exudative and proliferative processes. We are indebted to Klinge in particular for renewed interest in this phase of the rheumatic inflammatory response. In 1933 he emphasized that the importance of this primary rheumatic injury becomes apparent only by the systematic study of the rheumatic injury as it occurs in other parts of the heart, particularly the pericardium, and in other structures such as the synovial membranes, periarticular connective tissues and skin where the early alterative phase is better developed.

Of great importance also to an understanding of the significance of the rheumatic injury is the concept that the lesions pass through successive stages of development (Klinge, 1933; Gross and Ehrlich, 1934) and that the age of any particular lesion can be estimated by its histologic features It must be recognized, however, that interpretation of the life cycle of these lesions must be qualified by the knowledge that reactions to the rheumatic injury vary with the severity of the infection, with the patient and with the organ involved. As Clawson (1929) in particular emphasized, the histologic characteristics of lesions within the same organ vary greatly in the extent to which the degenerative, exudative or the proliferative phases have developed. Thus alterative, exudative or proliferative types of reaction may predominate or all three may be present side by side. According to Andrei and Ravenna (1937), the time required for the development of the various stages cannot be accurately predicted by the histologic appearance of the lesion. They pointed out that no one knows how long a granuloma, for example, a tubercle, may persist and they expressed the belief that the presence of the Aschoff body is neither definite proof of active rheumatic carditis nor evidence that a phase of activity has occurred recently.



Figure VIII-2 Aschoff nodule Early stage with fibrinoid degeneration of the collagen
a Mallory's phosphotungstic acid-hematoxylin stain X 215
b Hematoxylin and eosin X 600

Early (Alterative) Stage. According to Klinge (1933), typical Aschoff bodies are not present in the myocardium of patients dying within the first few weeks after onset of rheumatic fever. The first observable phase in the development of the rheumatic nodule is swelling and edema of the connective tissue fibers (Figure VIII-2*a*. *b*), which stain intensely with eosin and become waxlike and refractile. Fusion may occur at the points where they cross one another. The altered tissue assumes



Figure VIII-3 (Same case as Figure VIII-2.) Aschoff nodule Early stage with fibrinoid degeneration of collagen Gomori's reticulum stain. X 580.

the staining characteristics of fibrin and this leads to the term "fibrinoid swelling" or "fibrinoid degeneration" of the collagen In the early stages of this process the individual fibrils of the connective tissue can be shown by silver impregnation to remain intact though separated as if by edema (Figure VIII-3). In later stages actual necrosis of the fibrils frequently occurs In the meshes between the fibers there are fibrin-like masses or precipitated protein. The cellular components of the nodule at this early stage are not increased in number but appear to be shrunken. Lymphocytes and plasma cells are usually present in variable numbers Variations in the relative numbers and in the arrangement of collagen fibers, cells and precipitated protein give rise to somewhat different histologic types of rheumatic nodules. Gross and Ehrlich (1934) have described small cell coronal and reticular types in this early stage.

In some instances the so-called fibrinoid degeneration may be absent but in other cases it may be so severe that it simulates a severe degenerative process which may be indistinguishable from that of acute septic processes. As Clawson (1929) has indicated, occasionally cellular exudation may be prominent in the lesion and abscesses may seem to be present.

The interpretation of the early alterative lesion (fibrinoid degeneration) has aroused some disagreement. Although Klinge and others described it as a true degenerative process of the connective tissue, some (Clark *et al.*, 1936; Graef *et al*, 1937) have held that the fibrin-like appearance and reaction of the tissue were due merely to exudation of plasma and infiltration of the connective tissue with fibrin. Others (Klemperer *et al*, 1942) have considered it a "coagulation" of the ground substance. According to Altshuler and Angevine (1949), the common feature of fibrinoid formation is the precipitation of the acid



Figure VIII-4. Aschoff nodule, granulomatous stage. Giant cells are evident. Hematoxylin and eosin *a* X 110 *b*. X 420



Figure VIII-5 Aschoff nodule, granulomatous stage Hematoxylin and eosin

a Central clumps of fibrin or necrotic collagen X 400.

b Giant cells with ragged cytoplasm and streamers X 960

mucopolysaccharide of the ground substance of the connective tissue The precipitant in some instances is probably an alkaline protein derived from the necrosis of tissue or the interaction of the tissue with a damaging agent

Granulomatous Stage. The second phase in the development of the Aschoff body is well advanced one month after the onset of the illness At this time proliferating and hypertrophied connective tissue cells and sometimes giant cells dominate the picture (Figure VIII-4*a*, *b*). The central portion of the nodule usually contains a small amount of swollen, fragmented and occasionally necrotic collagen and sometimes masses of fibrin (Figure VIII-5*a*). The large mononuclear and multinuclear cells usually have vesicular nuclei and a basophilic cytoplasm when stained with hematoxylin and eosin Characteristically, the cytoplasm has ragged edges and there may be pseudopods or streamers (Figure VIII-5*b*). With Pappenheim's pyronine-methyl-green stain the cytoplasm stains a brilliant red. The nuclei are often hypertrophied and may appear pyknotic, fibrocytoid or owl-eyed depending on the arrangement of the chromatin.

The owl-eyed appearance of the nucleus is a characteristic of the Anitschkow myocyte (1913). This particular cell also has been called "myocardial reticulocyte" (Ehrlich and Lapan, 1939) and "cardiac histiocyte" (Downey, 1941) It is normally found in the heart and its valves. On longitudinal section the nucleus of this cell is elliptic and vacuolated except for a serrated bar of chromatin in the center. Fine fibrillar structures extend at right angles from the central bar toward and in many cases to the nuclear membrane (Figure VIII-6*a*) In cross section the nucleus is round or nearly so and has a dark mass of chromatin in the center from which chromatin fibrillae extend, giving it an owl-eyed appearance. In normal hearts little cytoplasm is observed but when inflammation is present, cytoplasm appears in increasing amounts and stains more deeply with hematoxylin The Anitschkow myocyte is often the chief constituent of the reaction of the heart to injury and is particularly prominent in the rheumatic nodule (Clawson, 1941) It constitutes the most characteristic feature of the lesion and is sometimes called "Aschoff" cell (Boyd, 1944).

The giant cells in the lesion are smaller than those of tuberculous lesions or in foreign body granulomas. Their cytoplasm is less abundant and is slightly basophilic. Their nuclei are relatively large and lobular and exhibit marked polymorphism

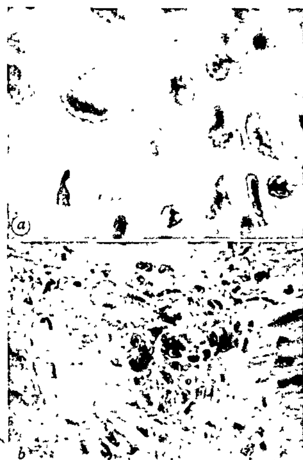


Figure VIII-6 Aschoff nodule, granulomatous stage Hematoxylin and eosin
a Anitschkow myocytes or myocardial reticulocytes X 1360
b Syncytial coronal type X 435

These giant cells are few in number, are located centrally *and are in close relation* to one another (Figure VIII-5*b*). In these features they resemble more closely the giant cells of Hodgkin's disease than those of tuberculosis Lymphocytes and plasma cells are to be seen in varying numbers together with an occasional polymorphonuclear leukocyte

This granulomatous phase of the rheumatic nodule is the one that is usually described in textbooks as typical of the Aschoff body. As Gross and Ehrlich (1934) emphasized, it is only when the nodule has reached this stage of development that certain diagnosis is possible and that the lesion is specific, differing from the lesions found in uncomplicated scarlet fever, subacute bacterial endocarditis or other inflammatory lesions of the heart.

The appearance of the rheumatic nodule varies with the extent of the proliferation of the characteristic cells and with their arrangement in relation to the altered connective tissue and the surrounding myocardial fibers. On the basis of those variations, Gross and Ehrlich recognize large cell coronal, syncytial coronal and mosaic types of Aschoff bodies in this stage. In the large cell coronal variety there is a central swollen mass of fragmented collagen and precipitated protein with increased numbers of characteristic Aschoff cells (Figures VIII-4 and VIII-5*a*). In the *syncytial* coronal type the central collagen is scant (Figure VIII-6*b*) but the cytoplasmic mass of the cells is greater, the cellular outlines are more indistinct and more cells are multinuclear. In the mosaic variety there is a more or less uniform distribution of collagen fibers and cells forming a mosaic pattern of the two components. This variety is observed most frequently.

Healing Stage (Three to Six Months). This third phase in the life cycle of the Aschoff body is dominated by regressive phenomena. The cytoplasm of the characteristic cells, although still basophilic, is *diminished in amount*, the outlines of the cells are sharp and the cells become spindle-shaped. Giant cells become scarce and the nuclei become fibrocytoid (Figure VIII-7*a*, *b*). The spindle-shaped cells become transformed into fibroblasts with delicate collagenous fibrils. The entire collection of cells begins to assume a definite direction within the planes of the myocardial bundles. The delicate collagenous fibrils fuse into dense collagenous bundles and the final stage is the development of the scar which characteristically lies between the muscle bundles. Peculiar onion-shaped scars which broaden the perivascular connective tissue and on whose edge some muscle fibers are de-

stroyed were described by Klinge (1933) as rheumatic in origin Occasionally they are visible grossly but usually they are microscopic in size. In 65 of 139 hearts from patients who previously had definite rheumatic fever or were suspected of having it, these perivascular scars were present (Wild, 1933). Their absence, of course, does not exclude a previous rheumatic inflammation According to Rossle (1935) and Morpurgo (1936), healing with the formation of a scar may follow the early alterative phase of inflammation without the development of the granulomatous stage.

Location. The rheumatic nodule is usually, but not always, found in association with blood vessels and is frequently found in relation to the adventitia of medium-sized or small arteries. Klinge (1933) traced 48 rheumatic nodules by serial sections and found that only five were unrelated to vessels. In the myocardium they are found most frequently in the interventricular septum and on the posterior wall of the left ventricle. The other most common sites in their order of frequency were the left posterior papillary muscle, pulmonary conus, posterior wall of the left atrium and the myocardial wedge between the aorta and left atrium. Clawson (1941) found them as frequently in the apex as in any other part of the heart.



Figure VIII-7 Aschoff nodules, healing stage Similarity of cells to fibroblasts should be noted Hematoxylin and eosin a X 30 b. X 85

Size and Shape. According to Geipel (1905), the rheumatic nodule can reach a length of 880 micra and a width of 80 micra. Clawson (1941) stated that marked variations were noted in the size of the nodules. They sometimes consisted of only a few cells near or surrounding blood vessels and sometimes they were large enough to extend entirely across a section more than a centimeter in width The nodule as described by Aschoff (1905) was rosette- or fan-shaped It tended to become elongated and irregular and to extend between the muscle fibers. According to Geipel, the nodules were round, oval or fusiform. Gross and Ehrlich (1934) described them as being occasionally spherical but generally ..., dishlike or spindle-shaped Klinge (19)33) stated that the nodule is usually spindle-shaped but often appears stretched longitudinally. Sometimes it is plump and ... The shape varies with the anatomic relationship and the amount and the extent of the space available Thus, between individual muscle fibers one finds small nodules whereas large ones are present in the larger connective tissue spaces

Frequency. Figures on the incidence of Aschoff bodies in hearts which are the sites of rheumatic inflammation vary from 32 per cent (Libman, 1923) to 95 per cent (Whitman and Eastlake, 1920). Clawson (1929) in a review of the incidence by



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a Anitschkow myocytes or myocardial reticulocytes X 1360

b Syncytial coronal type X 435

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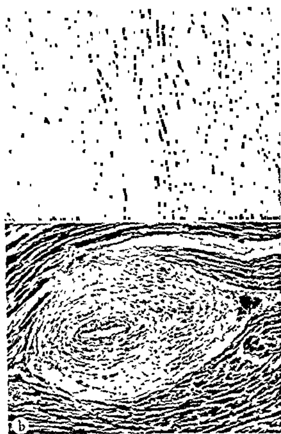


Figure VIII-7 Aschoff nodules, healing stage Similarity of cells to fibroblasts should be noted Hematoxylin and eosin *a* X 30 *b* X 65

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various investigators found that the mean incidence in 190 cases from various sources was 69 per cent.

Specificity. Since Aschoff's conclusion that the inflammatory nodules described by him were specific for rheumatic fever, most investigators have supported his views Noteworthy workers who held this opinion were Geipel (1905), Coombs (1909, 1924), Fraenkel (1912), Bracht and Wachter (1909), Huzella (1914), Thalhimer and Rothschild (1914), and Fahr (1921, 1930) More recently Gross and Ehrlich (1934) and Saphir (1941, 1942) have re-emphasized this view. In support of this opinion it has been stated that: (1) The nodules have distinctive histologic characteristics, (2) they are frequently encountered in acute rheumatic fever and infrequently in other acute infectious diseases, and (3) nodules of similar morphologic and staining characteristics have not been produced experimentally In opposition to this viewpoint, Clawson (1941) has held that the type of inflammation found in the rheumatic nodule in man cannot be said to be characteristic because of the following reasons (1) In a relatively high percentage of cases of acute rheumatic endocarditis the Aschoff nodules are not found in the myocardium; (2) they are not infrequently found in the heart in cases of nonrheumatic infectious disease, and (3) nodular areas with a cellular content similar morphologically have frequently been produced experimentally in rabbits by the injection of streptococci.

Regarding the second reason, Siegmund (1931), Muller (1933), Fahr (1930), Schmorl (1914), and Clawson (1941) have found similar proliferative nodular areas in the myocardium in cases of scarlet fever. Fahr (1930), who studied extensively the lesions occurring in scarlet fever, stated that in his investigation of streptococcic infections without rheumatic polyarthritis he never found a structure that could be identified as an Aschoff body. This was true of scarlet fever, streptococcic sepsis or streptococcic infection with diphtheria, and measles. Consequently, it still remains to be proved whether the lesions of scarlet fever are Aschoff bodies and, if they are, whether the patients have not had a previous rheumatic infection. Rosenblum and Rosenblum (1941) and Quinn (1947) stated that scarlet fever preceded the onset of rheumatic fever in 10 per cent and 16 per cent, respectively, of their patients.

In regard to the third reason, Saphir concluded that up to the time of his review in 1941 typical Aschoff bodies had not been produced experimentally. In 1943, however, Rich and Gregory were able to reproduce closely the five supposedly pathognomonic features of rheumatic carditis, including what they considered to be Aschoff bodies, in 11 of 36 rabbits by producing sensitization and anaphylactic phenomena with horse serum.

It is obvious that the specificity of the Aschoff body is a highly controversial subject Conclusions from the mass of conflicting data and opinions are difficult. It is my opinion that the typical Aschoff body in its fully developed granulomatous stage is as specific for rheumatic fever as the *tubercle is for tuberculosis.* Pathologists, however, are not satisfied with knowing the histologic reaction of the infectious agent but demand in addition that the causative agent be demonstrated by either histologic or cultural methods or by animal inoculation. Since this is not possible in the case of rheumatic fever, the demonstration of the typical rheumatic nodule in its granulomatous stage of development is the best evidence available on which the pathologist may base the diagnosis of rheumatic fever (Mallory and Keefer, 1941).

Diffuse Interstitial Myocarditis

Although diffuse rheumatic inflammation has received little attention compared to that given the rheumatic nodule, it may be of greater clinical importance Clawson (1940*a*) stated that it is present in about 18 per cent of cases of acute rheumatic myocarditis There are great variations in the extent and appearance of this inflammation. The lesions usually consist of edema of the connective tissue with such cellular elements as lymphocytes, plasma cells and macrophages. Occasionally many polymorphonuclear cells (Figure VIII-8*a*) may be seen and on rare occasions a predominance of eosinophils is noted (Watjen, 1921) The diffuse myocardial lesions are most prominent at the base of the valve leaflets. Romberg (1894) and Takayasu (1909) have described large epithelioid cells in the diffuse inflammation which have an identical appearance with the cells of the rheumatic nodule (Figure VIII-8*b*). Skworzoff (1938) has indicated that diffuse exudative inflammation either may be found about the specific rheumatic granuloma (a perifocal inflammation) or it may appear independently as a hyperergic reaction analogous to the exudative inflammation of joints and pericardium He was particularly impressed by the fact that patients who had extensive exudative lesions were usually children and presented an extraordinarily severe course with a clinical picture of myocarditis and a rapidly fatal outcome.



Figure VIII-8 Diffuse myocardial inflammation in rheumatic heart disease Hematoxylin and eosin
a Diffuse infiltration with polymorphonuclear cells X 160
b Diffuse inflammation with the presence of large basophilic cells X 105.

Direct Myocardial Damage

The discrepancy so frequently observed between the degree of functional impairment and the minor morphologic signs of inflammation demonstrable by the pathologist has led many to postulate and search for evidence of direct injury to the myocardial fibers The inadequacy of histologic methods to demonstrate such changes, so deplored by Coombs (1907, 1909, 1924) more than two decades ago, still remains.

Direct injury to the heart muscle is observed in the vicinity of the rheumatic nodules and has been interpreted to be the result of pressure atrophy of the muscle fibers (Figure VIII-9). Rich and Gregory in 1943 stated that necrosis of small foci of cardiac muscle occurs but that it is slight or absent in many of the less severe instances of rheumatic carditis. Such slight and nonspecific changes as cloudy swelling and waxy degeneration of the muscle fibers have been described. Coombs in 1924 stated that infiltration of the muscle



Figure VIII-9 Aschoff nodule with destruction of muscle fibers. Hematoxylin and eosin. X 160

cells with fat was the most definite phenomenon seen but it is not found in every case and it also is a feature of the later stages of the disease when active inflammation has subsided. Rarely, infarction of the myocardium is observed (Klinge, 1933) as a result of occlusion of a small vessel damaged by the rheumatic lesion. This may well be the explanation for a case of cardiac aneurysm reported by Parkinson and his associates in 1938 and attributed by Turnbull to rheumatic necrosis of the myocardium.

Lesions of the Conduction System

Impairment of the atrioventricular conduction is common during the course of acute rheumatic fever. The incidence of defects in conduction in this disease varies, with different authors, ranging from approximately 27 to 87 per cent (Bruenn, 1937). Reports of histologic studies of the bundle of His describe lymphocytic infiltrations in the region of the node and trunks, fibrous degeneration of the bundle of His with calcification and swelling of collagen. In active rheumatic fever Gross and Fried (1936) were able to demonstrate a variety of inflammatory and vascular phenomena in the conduction system by a few representative sections in 66 per cent of cases. It is probable that a study of more sections would have indicated a higher incidence. Few of these lesions were of a specific or highly characteristic nature. Aschoff bodies were found in the bundle of His in only two of the 60 cases of active rheumatic fever. Edema of the bundle was observed in only 15 per cent of cases. More frequently there were accumulations of lymphocytes and occasionally polymorphonuclear cells, plasma cells, macrophages and young fibroblasts. Vascular lesions, such as intimal thickening and hypertrophy of the media, were observed frequently and thrombosis rarely. In cases of inactive rheumatic fever few lesions were found in the bundle.

In view of the frequent occurrence of lesions of the conduction system it would seem unnecessary to ascribe impairment of atrioventricular conduction to either the direct effect of toxins on the conduction system or to an increase in vagal tone, as suggested by Bruenn.

ENDOCARDITIS

Valvular Inflammation

General Considerations. The term "endocarditis" has been used almost universally to denote the valvular lesion of rheumatic fever. Although thus honored by custom and usage even a cursory histologic examination of an affected valve reveals the inadequacy of the term. The basic lesion is not an endocarditis but an inflammatory process of the valve proper—a valvulitis with secondary involvement of the endocardial surface. In the descriptions of valvular lesions in this chapter the

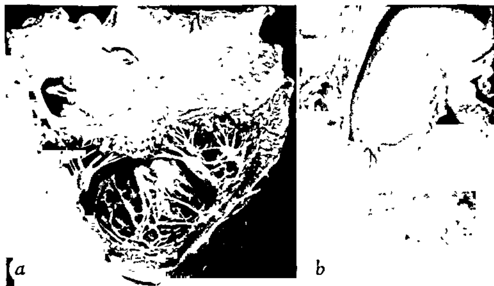


Figure VIII-10 *a* Acute rheumatic mitral endocarditis Verrucae on line of closure and involvement of left atrium
b Acute rheumatic aortic endocarditis

terminology used will be that outlined by Gross and Kugel in 1931 in their study of the topographic anatomy and histology of the valves of the human heart. In this volume the term cusps will be used to designate the component parts of a semilunar valve and leaflets, the component parts of an atrioventricular valve or of an unspecified valve

Gross evidence of rheumatic inflammation is commonly observed in the mitral and aortic valves, less frequently in the tricuspid and rarely in the pulmonary. Thus, Clawson (1945) reported that "of the 780 cases of rheumatic heart disease in which the valves were affected, there was involvement of the aortic or mitral or both valves in 779 (99.8 per cent)." In 44 (5 6 per cent) the valves on the right side of the heart were affected and in all of these, except one case in which a pulmonic valve only was affected, aortic or mitral involvement was associated (Clawson, 1940a). Histologic examination, however, discloses evidence of inflammation in the tricuspid valve as frequently as in the mitral and aortic (Gross and Friedberg, 1936).

Age and Sex. Disease of the mitral valve commonly occurs in youths and in persons of middle age and is more common in females than males in a ratio of three to two. Rheumatic disease of the aortic valve extends from early childhood to extreme old age. It is commonest in middle and old age and in males in about a ratio of three to one.

Acute and Subacute Valvulitis. *Incidence.* Clawson (1940a) studied 796 cases of rheumatic heart disease at necropsy and classified 98 as cases of acute rheumatic endocarditis (Table 1).

Gross appearance. The most conspicuous lesions in the early phases of valvular inflammation are the tiny translucent nodules (verrucae) which form along the lines of closure or contact (Figure VIII-10*a, b*) They vary in size from less than 1 mm to 3 mm. and are located on the atrial surface of the mitral and tricuspid valves and on the ventricular surface of the semilunar valves. Occasionally they are distributed elsewhere over the cusps. In later stages of the disease the nodules become more opaque and warty and are

reddish gray or tawny. They are firm and are not easily dislodged. They may be arranged simply in a row or in clusters of two or three. Occasionally they are fused for a considerable distance and form a pyramidal ridge along the line of closure. They may be observed also on the chordae tendineae and rarely on the papillary muscle. Not infrequently they extend over the posterior leaflet of the mitral valve and onto the endocardium of the left atrium. The nodules tend to form conglomerate mounds on the corpora arantii of the aortic valve and from there extend in rows along the semilunar cusps

Diffuse thickening of the valves with the exception of the pulmonic is a less conspicuous but frequent gross alteration The scalloped, concave margins of the atrioventricular valves are usually thickened and straight. Occasionally there is an irregular roughening and rarely slight vascularization of the atrial surface of the trioventricular valves The normally sharp rgin of the cusps of the aortic valve freuently becomes slightly thickened and rounded.

Histologic appearance The inflammatory process may be present in any portion of the leaflet but is observed most frequently in the proximal layers of the valve (auricularis layer of the atrioventricular valve and ventricular layer of the semilunar valves) with involvement of the spongiosa. Two varieties of inflammatory response may be observed which for descriptive purposes can be distinguished as nonspecific and specific (rheumatic) inflammation.

The nonspecific inflammatory process may involve the entire leaflet or cusp as well as the ring, and consists of edema, increased numbers of capillaries and a variety of inflammatory cells These cells are chiefly lymphocytes but occasionally polymorphonuclear cells predominate. Rarely these cells are so numerous as to suggest the presence of phlegmon (Klinge, 1933). Plasma cells, fibroblasts, macrophages and other mononuclear cells are often present in variable numbers.

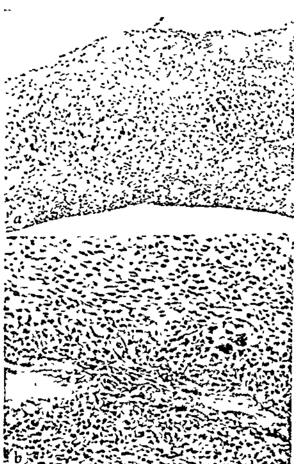


Figure VIII-11 Acute rheumatic valvulitis Hematoxylin and eosin

a Mitral valve. Focus of fibrinoid degeneration may be noted on proximal (atrial) surface and granulomatous nodules in the substance of the leaflet There is a suppurative reaction on the distal (ventricular) surface. X 95.

b Mitral valve. Bandlike zone of fibrinoid necrosis with giant cells. X 175.

If the inflammatory process presents only these features, it does not differ from valvulitis of other causes. In most cases, however, there is also, as Bulloch in 1908

described). These may be arranged in nodules or in rows and generally surround foci of intensely eosinophilic fragmented collagen (Figure VIII-11). This is the so-

called *fibrinoid swelling and degeneration* of collagen described by Neumann (1896) and emphasized in recent years by Klinge According to the latter, the fibrinoid swelling of the connective tissue is the primary injury to the valve and this may go on to degeneration and necrosis. The proliferative stage follows and consists largely of collections of the large Aschoff cells They may occur singly or after fusion, as with multinucleated giant cells In many cases the fibrinoid degeneration of the collagen occurs as a bandlike lesion, including a considerable portion of the leaflet (Figure VIII-11*b*). Not infrequently the band of fibrinoid degeneration is found directly beneath the endothelium of the proximal surface (Figure VIII-12). In these instances the proliferating cells may be found perpendicular to the altered collagen in a palisaded arrangement.

Gross and Friedberg in 1936 emphasized the occurrence of lesions in the valve rings in acute and subacute rheumatic fever The inflammatory process is similar to that in the leaflet and Aschoff bodies are present in the valve rings in approximately 10 per cent of cases in which the patient has died during the first attack of rheumatic fever The almost invariable presence and severity of lesions of the valve rings in the active stages of rheumatic fever, together with the



Figure VIII-12 Acute rheumatic pulmonary valvulitis *Granulomatous nodule in substance of cusp* Hematoxylin and eosin X 200





Figure VIII-13 Verrucae in acute rheumatic valvulitis Hematoxylin and eosin

a Granulomatous inflammation of substance of leaflet with a platelet and fibrin thrombus superimposed X 90

b Extruded portion of valvular collagen which has undergone fibrinoid degeneration X 150

fact that these rings may be the only part of the valve affected, suggested to Gross and Friedberg that this is probably the first portion of the valve leaflet involved by the rheumatic process In the great majority of their cases all the valves were involved, and involvement of only one or two valves was the exception.

Histologic appearance of verrucae These may have the appearance of platelet and fibrin thrombi deposited on the surface of the valve and staining intensely with eosin (Figure VIII-13*a*) or they may appear as an extruded portion of collagen which has undergone fibrinoid degeneration (Figure VIII-13*b*). In either case there is a marked

proliferation of fibroblasts in the region immediately adjacent to the vegetation, as well as edema and numerous lymphocytes.

Pathogenesis of verrucae. For a long time the viewpoint had been held that the pathologic changes in the valves consisted essentially of a piling up of thrombotic masses which came from the blood. Neumann in 1896, Bulloch in 1908, Coombs in 1909 and Swift in 1924 emphasized the appearance of the earliest changes in the subendothelial layers. Coombs stressed the predominance of the proliferative reaction in the valves and pointed out that the deeper structures reacted before there was evidence of injury to the endothelial surface. These observations led to the concept that damage to the deeper structures of the valve occurred first and the formation of vegetations followed later. Although this concept is now generally held (Clawson and Bell, 1926; Holsti, 1927-28; Darre and Albot, 1929, Shaw, 1929; Jaffé, 1938), the mode of production of verrucae is still disputed. Some workers believe verrucae to represent accumulations of platelets and fibrin (Leary, 1932; Hadfield and Garrod, 1947; Hall, 1948) Others consider verrucae to be the result of disintegration and fusion of proliferating cells on the superficial layers of the valve leaflets together with swelling and eosinophilic changes (Gross and Friedberg, 1936). According to Neumann (1896) and others, verrucae are extrusions of foci of fibrinoid degeneration and necrosis, while still others consider them to represent a combination of fibrinoid degeneration with deposits from the blood stream (Koniger, 1903). This latter view is in accord with most of my observations although in some instances I have confirmed Neumann's observations (Figure VIII-13*b*). The location and arrangement of the vegetations give clues as to their pathogenesis. The fact that their commonest site is the mitral valve and that they appear along its line of closure indicates their mode of formation. As Hadfield and Garrod (1947) have emphasized, the mitral valve closes against the highest pressure exerted anywhere in the circulatory system, and the impact of its surfaces and the mutual compression of those surfaces during systole constitute a degree of mechanical trauma which, although sustained without injury by a healthy endocardium, is sufficient to cause a breach of the surface when an inflammatory focus (the rheumatic nodule) lies immediately beneath it. The superficial destruction of endothelium occurs along the line of closure, and along this line also extrusion of collagen occurs and platelet thrombi may be deposited. The importance of high pressure and greater mechanical trauma are illustrated, according to Hadfield and Garrod, by the behavior of the valves on the right side of the heart. Vegetations are found on the tricuspid valve in only about 40 per cent of all cases; if this were due simply to the lower pressure on the right side of the heart, it would be expected that in conditions producing a rise of pressure on that side, tricuspid vegetations would be common. This is actually the case. If the disease recurs after mitral incompetence has been established, vegetations on the tricuspid and pulmonary valves are frequently found at necropsy.

Recurrent Valvulitis. *Incidence.* In the group of 796 cases of rheumatic fever studied at necropsy by Clawson (1940a), 76 cases (9.5 per cent) gave evidence of recurrent rheumatic valvulitis (Table VIII-1).

Gross appearance. As a result of repeated attacks of rheumatic fever gross alteration in the valves becomes more pronounced. Thickening, irregularity of the surface and gross vascularization are usually present and are most prominent in the mitral valve. With repeated attacks the thickening tends to become more severe

TABLE VIII-1

Types of Rheumatic Heart Disease Encountered in 796 Cases at Necropsy (From Clawson, 1940)

	Cases	Per Cent
Acute rheumatic endocarditis	98	12 3
Recurrent rheumatic endocarditis	76	9 5
Valve deformities	586	73 6
Incompletely healed	113	19 3
Completely healed	239 *	40 8
Calcified, nodular, aortic	234	39 3
Adherent pericardium	36	4 5

* See second footnote to Table VIII-2



Figure VIII-14 Recurrent mitral valvulitis
a Thickening of valve leaflet with prolongation over chordae tendineae
b Parallel rows of old and recent verrucae
c Recent verrucae on a previously damaged leaflet

in the distal third of the valve cusps. In the mitral valve the thickened tip may be prolonged over the insertions of the chordae tendineae (Figure VIII-14*a*). The chordae tendineae become thicker and shorter and the papillary muscles are much closer to the margins of the cusps. The thickening of the chordae tendineae is particularly prominent at their insertions into the leaflet where they appear to be absorbed into the latter. Verrucae in various stages of activity and healing may be observed. Sometimes they can be seen to be superimposed on a ridge of older verrucae at the line of closure and in other instances a parallel row of fresh verrucae can be discerned (Figure VIII-14*b*, *c*).

The aortic cusps, in addition to thickening, may reveal considerable shortening as a result of rolling and inversion of the free margins of the cusp toward the sinus pocket (Figure VIII-15*a*) The cusps may also present adhesions at the commissures and verrucae in various stages of activity. The latter may extend from one cusp to another across the commissures. Abnormalities in the valve pockets include verrucous ridges and folds An interesting feature of recurrent valvulitis is the higher incidence of verrucae on the valves of the right side of the heart (Figure VIII-15*b*) This may be related to the increased pressure in the pulmonary circulation following deformity and dysfunction of the mitral valve.

Histologic appearance Whereas the thickening of the valves in acute and subacute valvulitis is the result only of edema and inflammation, in recurrent valvulitis there is evidence of considerable fibrosis and elastic tissue proliferation in addition to inflammatory changes in various stages of activity. The inflammatory cells are predominantly lymphocytes with smaller numbers of polymorphonuclear cells, plasma cells and macrophages. The fibrosis and inflammation involve the rings as well



Figure VIII-15 Recurrent valvulitis
a Aortic valve Recent verrucae may be noted on a previously damaged cusp
b Tricuspid valve

as the leaflets, and the fibrous and elastic thickening is particularly prominent at the subvalvular angles. The intervalvular fibrous tissue is almost always involved also. In striking contrast to the appearance of acute valvulitis is the presence of numerous arteries with thick muscular walls in the ring and leaflet In cases of longer duration, walls of these vessels become fibrotic This increased vascularity is one of the most conspicuous features of recurrent valvulitis (Figure VIII-16*a*). Another distinct difference from the appearance of the leaflet in acute valvulitis is the marked fibrosis and thickening of its tips. There are usually more verrucae in recurrent valvulitis and many of them show evidence of organization. In the valve pockets the endocardium *is* usually *thickened,* and sometimes inflammatory polypoid vascular projections of the endocardium (Figure VIII-16*b*) are present (Gross and Friedberg, 1936). *In addition to these various* nonspecific signs of inflammation, Aschoff bodies frequently are found in the fibrosa or spongiosa layers of the leaflets.

Chronic Valvulitis. This condition is encountered at autopsy after one subsiding *or several recurrent bouts of rheumatic* fever without recent exacerbation. In other words the end results, usually of repeated attacks, of rheumatic inflammation may be noted and the last attack before death may be subsiding but the lesion has not *yet completely healed.* This concept is in accord with the idea that rheumatic fever

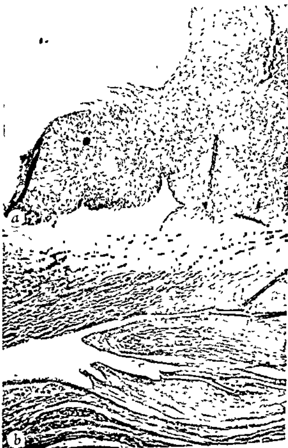


Figure VIII-16 Recurrent rheumatic valvulitis. Hematoxylin and eosin
a. Tip of mitral valve X 50
b. Polypoid projections in subvalvular angle. X 60.

is a disease of recurrent acute attacks rather than a sustained chronic inflammatory process.

Incidence. In 113 of 796 cases of rheumatic heart disease Clawson (1940a) found valvular deformities which were incompletely healed (Table VIII-1) In four of these 113 cases the aortic valve was involved alone, in 65 the mitral alone, in 28 the aortic and mitral valves were involved, in eight the aortic, mitral and tricuspid, in one the *aortic, mitral, tricuspid* and pulmonic and in seven the mitral and tricuspid (Table VIII-2)

TABLE VIII-2

Combinations of Valve Involvement in 779 Subjects with Rheumatic Heart Disease (From Clawson, 1940)

	*A**	*M*	*T*	*P*	*AM*	*AT*	*AP*	*AMT*	*AMP*	*AMTP*	*MT*	*MTP*	*TP*	*Total*
Acute rheumatic	2	43	0	1	24	0	0	10	0	9	9	0	0	98
Recurrent rheumatic	2	21	0	0	30	1	0	11	1	4	6	0	0	76
Valve deformities:														
Incompletely healed	4	65	0	0	28	0	0	8	0	1	7	0	0	113
Completely healed	17	149	0	1	45	0	0	17	0	0	9	0	0	238†
Calcified, nodular, aortic	136	0	0	0	92	1	0	5	0	0	0	0	0	234
Adherent pericardium	6	11	0	0	2	0	0	1	0	0	0	0	0	20
Totals	167	289	0	2	221	2	0	52	1	14	31	0	0	779

* A, M, T P, represent first letters of valves affected
† Clawson reported data on only 238, not on 239 cases indicated in Table VIII-1

Gross appearance. The changes already described in recurrent valvulitis are present and are more advanced in cases of chronic valvulitis (*Figure VIII-17a, b*) Usually the thickening and fibrosis have resulted *in a loss of elasticity* and narrowing *of the orifice.* Occasionally retraction and *curling have led to more* insufficiency than stenosis (Clawson, Bell and Hartzell, 1926). Thickening, fusion, absorption and shortening of the chordae tendineae are severe and not infrequently the papillary *muscles are almost in* contact with the margins extend from the leaflet to the ventricular wall and obliterate the angle. The regions of the valve rings and the subvalvular angles are thickened and prominent.

In addition to severe *diffuse thickening* of the leaflets there is evidence of deposition of calcium salts These deposits may further distort the leaflets and may project through to the atrial and ventricular surfaces In the aortic valve the calcium is found in the region of the noduli and in the commissure as well as *in the cusps* themselves As a result there is much *more* distortion than in acute or recurrent inflammation and the cusps *are rigid*

The rheumatic verrucae are less frequent than in recurrent valvulitis and are broad and flat Occasionally nonspecific vegetations are found on valves which are the seat of chronic *inflammation,* as well as *in* completely healed deformed valves *These* vegetations consist essentially *of* noninfected thrombi and are not related to active rheumatic inflammation. They are usually flat and they form on the line of closure or on calcified or ulcerated areas unrelated to the line of closure.

Histologic appearance. Signs of *active* inflammation are less pronounced than in recurrent valvulitis The thickening which is apparent *grossly* can be seen to be due to increased fibrous and elastic tissue *throughout the entire* leaflet *including the* rings as well as the tips of the





Figure VIII-17. Chronic valvulitis
a Mitral valve with severe stenosis of orifice Note greatly enlarged left atrium Thickening and deformity of leaflets and thickening and shortening of chordae tendineae.
b Aortic valve Fusion of cusps and rolling of the free margins are noticeable.

phocytes and other inflammatory cells tend to disappear and the fibrous connective tissue has become more homogeneous and hyaline (Figure VIII-18*a*).

In the valve rings the annulus frequently is hyalinized. The posterior mitral leaflet frequently reveals the greatest thickening but active inflammation is more likely to be noted in the tricuspid leaflets. All valves are vascularized by capillaries and thick-walled vessels which are more numerous on the superficial layers (Figures VIII-18*b* and VIII-19). Calcification is common in the leaflets and the lime salts may be distributed diffusely or in the form of large nodular masses. In the ring the annulus may reveal calcification and formation of bone.





Figure VIII-18. Chronic mitral valvulitis Hematoxylin and eosin.
a Note fibrosis and paucity of inflammatory cells X 8. *b* X 85.



Figure VIII-19. Chronic aortic valvulitis. Hematoxylin and eosin. X 22. Compare with Figure VIII-18*a*.

The verrucae are organized by fibroblasts and there are many new collagenous fibers. As healing progresses, the fibroblasts decrease in size and finally disappear altogether The central part of the verrucae becomes a scar-like structure. The thrombotic vegetations which form on the line of closure of the valves and on calcified and ulcerated portions of the deformed valves have a hyaline appearance and seem to be formed largely of platelets. There is little or no cellular reaction at the base. They rest on the scarlike hyaline connective tissue of the leaflet and the thrombus shows little or no tendency toward organization

Healed Valvulitis (Valvular Deformities)

In this section deformities which result from rheumatic inflammation will be considered. It should be emphasized, however, that not all valvular deformities are rheumatic in origin. When a valvular deformity is encountered either in the clinic or at necropsy the clinical or morphologic data may not give sufficient evidence so that the etiologic factors involved can be determined satisfactorily At present the tendency is to consider all such lesions, particularly when the mitral valve is affected, as rheumatic in origin The wisdom of such dogmatism may well be questioned It does not seem that enough is known concerning the valvular damage in a wide variety of toxic, infectious and metabolic processes to dismiss all etiologic possibilities except rheumatic fever in the interpretation of any valvular deformity.

In this connection such studies as those of Baldassari (1909), Czirer (1913) and de Vecchi (1931) should be mentioned. These investigators found histologic evidence of acute valvulitis in children in the presence of such diverse diseases as scarlet fever, diphtheria, bronchopneumonia, meningitis and tuberculosis without gross evidence of valvular damage From these studies it seems possible that patients, especially children, who survive such infectious processes also have acute valvulitis which in some instances may heal and result in valvular deformities. The same may be postulated for the healed stage of bacterial endocarditis (Saphir, 1941, 1942; Moore, 1946). The scarred end-stage of any inflammatory process rarely gives pathognomonic signs of the original etiologic agent. It would seem, therefore, that in instances in which there is neither good clinical nor pathologic evidence of previous rheumatic disease caution should be exercised in the interpretation of valvular deformities. It would seem that in such instances more will be gained by withholding judgment and carrying on further investigation than by arriving at more or less dogmatic conclusions.

General Considerations. The healing of acute rheumatic endocarditis may leave no grossly demonstrable defect in form or function or may leave merely a slight thickening of the valve leaflets along the line of closure The number of valves affected and the degree of scarring and deformity vary greatly with the number and severity of previous attacks as well as the age at which death occurs The valvular scars and deformities are for the most part the result of valvular inflammation and only in small part due to organization of vegetations. Organization of thrombi and contraction may be an important explanation of some deformities but the importance of cellular proliferation in the valve itself is often underestimated. The scar forms as a result of fibroblastic proliferation and collagen formation, lipoid deposition and calcification occur later.

General Incidence. Although not all valvular deformities are rheumatic in origin it is generally agreed that most of them are Of 73 cases in which old deformed valves were present 55 were found to re-

sult from rheumatic endocarditis, and in 27 of these 55, incompletely healed rheumatic lesions were recognizable (Clawson and Bell, 1926). The greatest number of deaths resulting from rheumatic heart disease occur in the group of cases in which valvular deformities are present (73.5 per cent of 796 cases, Clawson, 1940*a*). According to Clawson the incidence of involvement of each valve in 351 cases in which there were valvular deformities was as follows: aortic alone 21 cases, mitral alone 214 cases, aortic and mitral 73 cases, aortic, mitral and tricuspid 25 cases, mitral and tricuspid 16 cases, pulmonic valve one case and all valves one case (Table VIII-2). These figures do not include 234 cases in which calcified nodular aortic lesions were found. In this latter group there were 92 cases in which aortic and mitral valves were involved and five cases in which aortic, mitral and tricuspid valves were involved

Deformities of the Mitral Valve. These are observed commonly in young and middle-aged persons and less commonly in the old Females show a greater tendency to deformity of the mitral valve than do males, the ratio is about 3.2 (White, 1944).

Mitral stenosis. Stenosis of the mitral orifice is the most common type of deformity It results from fusion of the leaflets at their edges and fusion and shortening of the chordae tendineae. On examination from the open left atrium, this lesion has a characteristic diaphragmatic or funnel shape (Figure VIII-20*a*, *b*). The walls of the funnel are formed by the fused leaflets of the valve which lead down to a small opening of variable shape. This opening has received such names as "buttonhole" or "fish mouth." Calcium salts, either diffusely distributed or deposited in nodular masses, are frequently present in the thickened leaflets. The latter sometimes erode the endocardium and are exposed to the blood stream. Sometimes there is calcification of





Figure VIII-20. Stenosis of orifice of mitral valve.
a Fusion and calcification of leaflets with stenosis of orifice
b Stenosis of mitral orifice and mural thrombi in left atrium.

the ring with or without simultaneous involvement of the leaflet. The leaflets may be so adherent and rigid that the movement necessary for their apposition is not possible. Consequently valvular insufficiency is present, as well as stenosis of the orifice. According to White (1944), mitral stenosis and mitral regurgitation are almost

invariably combined. In rare instances, however, one may occur without the other. (1) When retraction of the relatively undamaged or at least relatively nonadherent valve leaflets is caused by shortened, contracted and perhaps fused chordae tendineae, mitral regurgitation may occur without stenosis. (2) When the valve leaflets are fused at the commissures, stenosis of the mitral orifice may occur without sufficient fibrosis or thickening of the extremities of the leaflets, or shortening of the cordae tendineae, to allow regurgitation. Pure stenosis (extreme stenosis with only slight insufficiency) was present in 37 of 95 cases of disease of the mitral valve reported by Clawson, Bell and Hartzell, in 1926. Severe degrees of rheumatic mitral stenosis are observed more frequently than severe degrees of mitral incompetence and are apparently borne better (White). The development of stenosis of the mitral orifice is a gradual process and the earliest defect in rheumatic children is insufficiency rather than stenosis. According to White, it requires at least two years for the development of mitral stenosis.

When stenosis of the mitral valve is present, the ring and leaflets are microscopically composed of dense fibrous tissue which is usually hyaline in appearance All signs of active inflammation are absent except occasionally a little perivascular lymphocytic infiltration in the central part of the leaflets. There is extensive vascularization of the leaflet and annulus fibrosus by capillaries and extremely thick-walled vessels with narrow lumina.

Effects of mitral stenosis on the heart. In the presence of a stenotic mitral orifice the left atrium and the right ventricle reveal evidence of hypertrophy and dilatation The left atrial enlargement may be so extreme that the heart may appear to be merely an appendage to an atrial aneurysm. These changes are of course the result of the increased effort required to force the blood through the narrowed mitral opening and by the resulting obstruction to the pulmonary circulation. The degree of stenosis alone probably does not account for such cases of extreme atrial enlargement but rather the combined effect of mitral regurgitation, mitral stenosis, the dilatation that comes with atrial (auricular) fibrillation and other factors not well understood. In 16 of a series of 26 cases of large left atria found at necropsy at the Massachusetts General Hospital, mitral stenosis was present and in 10 mitral insufficiency without stenosis was present (White, 1944).

Mural thrombi, particularly in the auricular appendage or atrium, are likely to form in the later stages of the disease when the atria fibrillate (Figure VIII-20c). Pedunculated thrombi and free or ball-thrombi are rarely found. When present, they may mechanically obstruct the circulation, causing marked feebleness of the pulse and syncope.

The right atrium eventually also may become hypertrophied and dilated if the right ventricular dilatation results in tricuspid regurgitation. The left ventricle may show no evidence of hypertrophy even when the right ventricle and left atrium are double their normal size, in fact the left ventricle may be a little smaller than normal as a result of diminished work. The apex of the heart is sometimes formed in large part by the right ventricle.

Occasionally angina pectoris occurs in cases of uncomplicated mitral stenosis According to Blackford (1940), this is the result of a failing heart muscle The right ventricle and left atrium, which are taxed to force blood through the stenosed mitral orifice, are unable to meet unusual demands, the left ventricle, therefore, is unable to sustain a high enough pressure in the root of the aorta to supply the coronary arteries with a sufficient amount of oxygenated blood.

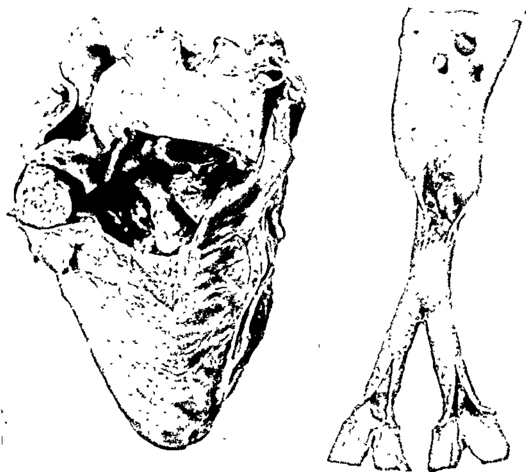


Figure VIII-20 c Stenosis of mitral orifice and thrombosis of left auricular appendage producing embolism to abdominal aorta with resulting gangrene of both lower extremities (WCGH, 39 A 36.)

Although the point is still disputed, a *number of authors agree that the factor* precipitating cardiac failure in patients who have old rheumatic heart disease is *often reactivation of the rheumatic myo*carditis (Rogers and Robbins, 1947).

Mitral insufficiency. Since stenosis of *the orifice and insufficiency of the valve* are generally combined to a greater or lesser degree in cases of rheumatic mitral disease, *the effects on the heart depend in part on* the relative amounts of stenosis and regurgitation and in part on the absolute degree *of valvular disease. If mitral insufficiency* is the chief defect (Figure VIII-21), hypertrophy of the left ventricle occurs as well as *enlargement of the left atrium and* right ventricle. Later there may be hypertrophy and dilatation of the right atrium. *With severe and longstanding mitral* insufficiency the size of the heart may become enormous.

Aside from hypertrophy, the heart muscle in deformities of the mitral valve may be normal, or there may be perivascular *scars suggestive of healed Aschoff bodies.* In cases of valvular deformity of long standing, the myocardium may become ex*hausted and fail without evidence of* pathologic change unless there is a complication such as recurrence of rheumatic inflamma*tion, bacterial endocarditis or* serious disease of the coronary arteries. It is frequently the valvular lesion and not the *myocardial disease that* eventually causes failure and death.



Figure VIII-21 Fibrosing lesions causing mitral insufficiency

Effects of mitral deformities on other organs. In the presence of mitral deformities the lungs, and later the liver and other organs, reveal evidence of chronic passive hyperemia. The distended pulmonary capillaries and bronchial veins (Ferguson *et al*, 1944) may rupture, giving rise to hemoptysis Areas of hemorrhage and infarction are found particularly at the bases of the lungs, and phagocytes filled with hemosiderin form a prominent feature of the histologic appearance. When deposits of iron pigment are sufficiently extensive, the lungs have a brownish hue and the condition is known as brown induration of the lung. Parker and Weiss (1936) pointed out that in addition to engorgement and thickening of the walls of the capillaries and arterioles permanent changes in structure occur in the alveolar walls (Figure VIII-22*a*), which may become twenty times thicker than normal. The basement membrane of the capillary endothelium becomes thickened and separated from that of the alveolar epithelium by interstitial edema and collagen. There is intimal thickening of the pulmonary arteries with hyperplastic arteriolar sclerosis (Figure VIII-22*b*). All these changes seriously restrict gaseous interchange so that intense cyanosis may persist in spite of myocardial improvement

Deformities of the Aortic Valve. The changes that may occur as a result of repeated attacks of rheumatic inflammation have already been described under recurrent and chronic valvulitis. Suffice it to state here that adhesions of the cusps at the commissures, thickening, fibrosis and calcification of the ring and cusps lead to stenosis of varying degrees (Figure VIII-23*a*, *c*). Scarring, retraction and stiffening of the free borders of the leaflets, however, result in insufficiency or regurgitation (Figure VIII-23*b*, *d*) of the mitral valve; here also rheumatic inflammation causes both stenosis and regurgitation; it rarely gives rise to regurgitation alone except in the earliest stages, and also rarely to stenosis alone. The end result of repeated attacks of rheumatic disease may be preponderant aortic stenosis, preponderant



Figure VIII-22 Pulmonary lesions in mitral stenosis.
a Congestion, edema and fibrosis of alveolar walls Hematoxylin and eosin. X 165.
b Intimal fibrosis and medial hypertrophy of arteries. Elastin-van Gieson. X 125.

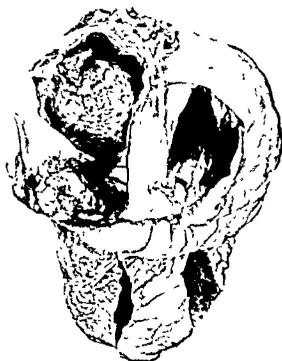


Figure VIII-22 c Ball-valve thrombus in left atrium in heart with stenosis of mitral orifice Dorsal view of heart (WCGH, 40 A 466)

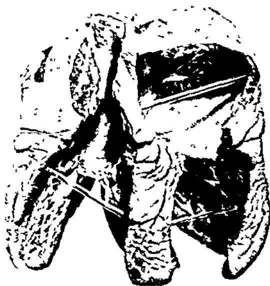


Figure VIII-22. *d* Stenosis of orifice of mitral and tricuspid valves. Dilatation of right atrium Obstructing mural thrombus left atrium which was responsible for cyanosis. Heart viewed dorsally (WCGH, 33 A 4.)

aortic regurgitation or equal degrees of both (White, 1944).

In Cabot's series (1926) of 152 cases of aortic valvular disease there were 93 cases of stenosis and regurgitation of the aortic valve of rheumatic origin and 11 cases of regurgitation with little or no stenosis, of which only six proved to be of rheumatic origin. Most of the cases with aortic regurgitation without stenosis were syphilitic in origin (44 cases). In a group of 130 cases of old valvular defects studied by Clawson and associates in 1926, 41 revealed combined stenosis of the orifice and insufficiency of the aortic valve. In 13 of these 41 cases insufficiency was the dominant defect.

Aortic stenosis. According to Clawson, Noble and Lufkin (1938), aortic stenosis *is a common form of heart disease. It com*prises 40 per cent of all deformities of the valves. It occurs chiefly in males in a ratio of 4:1 (Dry and Willius, 1939). The average age at death is 15 to 20 years more than in cases of mitral stenosis. The usual form of aortic stenosis is the calcific nodular type. The orifice is reduced to a narrow *rounded or triangular opening* and the cusps contain massive calcified nodules. The calcified masses usually are found on both surfaces of the cusps. Occasionally they are observed only on the aortic surface and rarely only on the *ventricular* surface. Microscopically the deposits of calcium are usually associated with a proliferative type of inflammatory process which is not always in immediate relation to the location of the calcium. *Often the* most pronounced inflammation is seen in parts of the scar where there is no calcium. The calcium is usually embedded in scar tissue near thick-walled vessels. Vascularization of the valve and the ring is *usually* observed.

It is at times extremely difficult to make a decision concerning the etiologic factor in cases of aortic stenosis. When the lesion

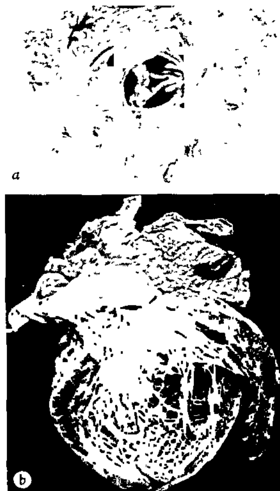
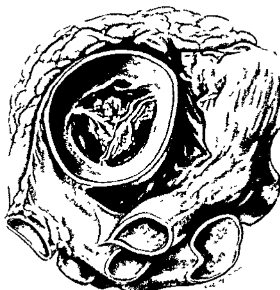
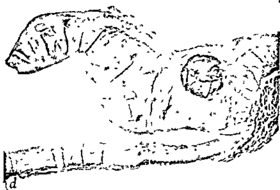


Figure VIII-23 Deformities of aortic valve
a Stenosis of aortic orifice
b Aortic insufficiency with regurgitant (diastolic) endocardial pocket in lower portion of figure





c Calcific sclerosis with bicuspid formation of aortic valve (Drawing by Louise Horne, Wayne County General Hospital, WCGH, 45 A 180)
d Fibrosis and calcification Hematoxylin and eosin X 7

is associated with a clear-cut history of rheumatic fever or an associated deformity of the mitral valve, rheumatic inflammation appears likely When it is not associated with other valvular deformities, some investigators (Monckeberg, 1904, Sohvol and Gross, 1936, Ashworth, 1946, Hultgren, 1948) have concluded that degenerative or metabolic factors are responsible Sohvol and Gross, and Hultgren were unable to find stigmata of rheumatic fever in most of the hearts with calcific disease of the aortic valve According to Ashworth, the factors to be considered in the development of atherosclerosis of the heart valves are age, hypertension, the physiologic decrease in cellularity of the annulus fibrosus of the aortic and mitral valves, and the effect of tension and vibration on certain portions of the valves Other investigators (Hall and Ichioka, 1940; Karsner and Koletsky, 1947) have concluded that rheumatic inflammation is always the basis of the deformity This assumption is based on the incidence of rheumatic fever in the history of patients with this deformity, the numerous transitions found between

doubtedly healed rheumatic lesions and calcified nodular valves, and the association of other lesions also probably caused by rheumatic fever.

My views on this problem have been indicated in the general considerations of the subject of valvular deformities. It seems to me that although calcific disease of the aortic valve in most cases is rheumatic in origin, knowledge of the early stages of this deformity is not complete enough to permit one to consider rheumatic injury to be responsible for this condition in all cases

Effect of aortic stenosis on the heart In cases in which aortic stenosis is not associated with regurgitation the left ventricle is tremendously hypertrophied and there is little or no dilatation until the heart has begun to fail The right ventricle may appear to be a mere appendage to the left, the wall of the latter bulges markedly into the cavity of the former. The other chambers of the heart are unaffected until cardiac failure sets in and then dilatation of the right side of the heart will occur. The degree of atherosclerosis of the ascending aorta and coronary arteries varies inversely with the degree of aortic stenosis. This suggests that the stenosis develops early in life and protects the aorta against the normal fluctuations of blood pressure.

Cause of death in aortic stenosis. Aortic stenosis is apparently better tolerated than other varieties of valvular deformity. Although severe stenosis of the aortic orifice is a serious burden on the heart, it is a lighter one than aortic regurgitation. This is indicated by the fact that in most cases aortic stenosis does not come to the attention of physicians or is not encountered at necropsy until the person affected is relatively old. Death is associated with congestive failure in about one-third of the cases. Sudden death occurs in about one-fifth of the cases and when all grades of stenosis are considered, death seems to result from noncardiac causes in about one-half of the cases (Dry and Willius, 1939). Although coronary occlusion is extremely rare, angina pectoris is a symptom in 19 per cent of cases according to McGinn and White (1934) and in 22.7 per cent according to Contratto and Levine (1937). This symptom has been explained as being the result of myocardial ischemia. The latter has been attributed to the stenotic orifice, the increase in cardiac work and also to vasomotor changes in the caliber of the coronary vessels (Harrison, 1937). Contratto and Levine have pointed out the likeness of the aorta and coronary system in these cases to the common water-faucet suction pump and have suggested that the negative pressure produced may interfere with coronary flow.

Disturbances in atrioventricular conduction also are often associated with calcific aortic stenosis (Boas, 1935). These are the result of an extension of the calcific process into the annulus fibrosus or ventricular septum. Associated mitral stenosis seriously militates against maintenance of cardiac function in cases of aortic stenosis.

Aortic insufficiency. Insufficiency results when there is curling and retraction of the cusps. Marked aortic regurgitation has a more rapidly serious effect than marked aortic stenosis. The heart becomes very large and left ventricular hypertrophy and compensatory dilatation apparently develop simultaneously. Hearts which weigh 1000 grams or more have been observed The largest and heaviest hearts generally occur in the presence of pure aortic regurgitation. The regurgitation is most often a complication of syphilitic aortitis but occasionally results from rheumatic infection. When the left ventricle dilates tremendously as a result of aortic regurgitation, the mitral valve becomes incompetent, and hypertrophy and dilatation of the left atrium ensue These are followed in turn by enlargement of the right ventricle and

eventually by enlargement of the right atrium too, though death due to left ventricular failure is likely to interrupt the full evolution of these various steps (White, 1944). In addition to the extensive hypertrophy and dilatation with flattening of the trabeculae carneae, endocardial pockets also may result from the regurgitant blood stream (Figure VIII-23*b*); aside from these changes, the myocardium may reveal no lesion. Apparently the hypertrophied muscle fails under the strain of overwork which is caused by the valvular deformity Another factor in bringing about myocardial failure may be the low diastolic pressure which in turn is the result of the aortic insufficiency. Normally the coronary circulation is maintained by a sufficient diastolic pressure. The frequent occurrence of angina pectoris in cases of advanced aortic stenosis also suggests the importance of functional coronary insufficiency. Aside from focal fibrosis of the myocardium, however, there is usually no morphologic evidence of myocardial ischemia. Dilatation of the ascending aorta occurs but is not as common in cases of rheumatic aortic regurgitation as it is in cases of regurgitation resulting from syphilitic valvulitis and aortitis.

Deformities of the Tricuspid Valve. Evidence of inflammation can be found as frequently in the tricuspid valves as in the mitral and aortic valves (Gross and Friedberg, 1936). Deformities of the tricuspid valve, however, are rare and seldom occur without lesions in other valves. From 4300 necropsies performed at the Massachusetts General Hospital, 217 cases of rheumatic heart disease and only 47 lesions of the tricuspid valve were described. Only 30 of these 47 lesions were tricuspid stenosis of sufficient degree to be considered of clinical importance (Cooke and White, 1941) In a study of 351 cases of old valvular deformities (Table VIII-2), Clawson was unable to find a single instance in which the tricuspid valve alone was involved. It was involved, however, in 42 cases in association with other valvular lesions. The age and sex incidence of the patients whose tricuspid valves were deformed corresponded roughly to those of patients who have mitral stenosis. Children and young adults were affected, and females were affected slightly more frequently than males. The average age at death was much less than that in all cases of rheumatic heart disease. In Cooke and White's series it was 23 years as compared with 42 years for rheumatic heart disease in general.

Valvular insufficiency and stenosis of the orifice are almost invariably associated with deformities of the tricuspid valve although one or the other may predominate. According to White, stenosis becomes of clinical importance when the circumference of the adult tricuspid ostium (normally 11 to 13 cm.) is reduced to 8 cm. or less (Figure VIII-24*a*, *b*) Functional tricuspid insufficiency is common in association with right ventricular dilatation associated with congestive heart failure and is rarely associated with other factors like anemia and pulmonary insufficiency.

Effect on the heart Because deformities of other valves are practically always associated with deformities of the tricuspid valve a combination of effects is noted on the cardiac chambers. Well-marked tricuspid stenosis, if uncomplicated, naturally affects little of the heart except the right atrium, which becomes enlarged. Tricuspid stenosis acts wholly on the circulation as a process obstructing the return of blood to the heart and is comparable to the effect of chronic constrictive pericarditis Tricuspid insufficiency results in hypertrophy and dilatation of right atrium and ventricle. According to Cooke and White, the presence of deformity of the tricuspid valve signifies a more severe degree of heart disease than deformity of



Figure VIII-24 Deformities of tricuspid valve. *a.* Insufficiency with stenosis of orifice. *b.* Stenosis of tricuspid orifice (valve opened)

mitral or mitral and aortic valves and consequently death comes much earlier. However, after systemic venous congestion sets in, life lasts longer when stenosis of the tricuspid orifice is present than when it is not, because of the protection afforded to the heart and lungs by the mechanical obstruction of the stenosis. Consequently tricuspid stenosis is similar to chronic constrictive pericarditis in that it produces a cardiac invalid who may live for years; he may have little dyspnea despite hepatic enlargement and ascites This long course is in contrast to the shorter course of life in cases of pure mitral stenosis after congestive failure has set in

Deformities of the Pulmonary Valve. Acute rheumatic inflammation of the pulmonary valves (Figure VIII-12*c*) occurs not infrequently (Gross and Friedberg, 1936) in association with involvement of other valves but apparently leads to deformity only rarely (two cases out of a total of 351 cases of valvular deformities reported by Clawson, 1940a). As a result of deformities of the pulmonary valve, hypertrophy of the right ventricle, and later, dilatation with signs of congestive failure develop. The right atrium also is usually enlarged.

Mural Endocarditis

Lesions of the mural or parietal endocardium in rheumatic fever are seen most commonly in the left atrium. Although these lesions had been previously noted and described (Huchard, 1903; Harper, 1914; Hertel, 1920), they did not attract much attention until MacCallum's classic description in 1924.

Lesions of the Left Atrium. *Incidence.* Von Glahn (1926) found these lesions in nine (29 per cent) of 31 cases, Thayer (1925) in 10 (40 per cent) of 25 cases and Gross (1935b) in 70 (80 per cent) of 87 cases.

Gross appearance. The lesion of mural endocarditis is usually observed just above the posterior leaflet of the mitral valve (Figure VIII-25). It is usually about 3 cm. in greatest extent but may involve almost the entire endocardial surface and extend into the auricular appendage and up to the orifices of the pulmonary veins. The



Figure VIII-25 Endocarditis of left atrium Severe mitral valvulitis of rheumatic type (WCGH, 43 P 43E)

wall of the atrium is markedly thickened and made irregular by low ridges and hillocks separated by furrows with no definite pattern (Von Glahn) Occasionally the irregular furrowed appearance is absent and there are only flat, often rounded, plateaus sometimes measuring no more than 2 mm in diameter (Gross). On rare occasions distinct projections may be seen which resemble vegetations. In cases of acute mural endocarditis the lesion has a tawny gray color, it is grayer and more translucent in the older lesions. In these older lesions the patch may appear dense and scarlike. It rarely is calcified (Stewart and Branch, 1924).

Histologic appearance of acute lesions. In these lesions as in the acute valvulitis the inflammatory process consists of characteristic and noncharacteristic components. The characteristic components consist of more or less typical Aschoff bodies which seem to have a predilection for the subendocardial layers. Usually these structures are forced into bands or rows of palisaded cells on either side of swollen collagen fibrils in various stages of fibrinoid degeneration (Figure VIII-26*a*, *b*). The nuclei are arranged perpendicularly to the altered collagen and the appearance is like that observed in some instances in the valve leaflets. Frequently the band of fibrinoid degeneration coincides with the layer of connective tissue immediately beneath the endothelium. In some instances there is fibrinoid degeneration of the subendothelial connective tissue without any cells or with only a few cells arranged about it

Among the indications of nonspecific inflammation are edema and marked infiltration of mononuclear cells, mostly lymphocytes. Polymorphonuclear cells,



Figure VIII-26 Lesions of mural endocardium
a Bandlike zone of fibrinoid degeneration with palisaded basophilic cells. Hematoxylin and eosin. X 135
b Healed stage Increased collagenous and elastin fibrils Elastin-van Gieson X 95.



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b. Healed stage. Increased collagenous and elastin fibrils Elastin-van Gieson X 95.

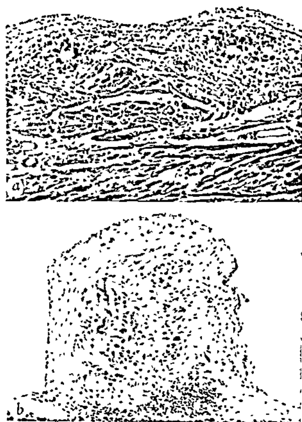


Figure VIII-27 Lesions of left ventricle Hematoxylin and eosin
a Mural endocarditis X 135
b Verruca of endocardium X 145

including the eosinophilic variety, are present occasionally, and rarely polymorphonuclear cells may be predominant in the inflammatory exudate These cellular aggregations are found in any portion of the endocardium but are perhaps more often present in the inner half. They separate and distort the elastic fibers and are often the cause of the ridges and hillocks on the endocardial surface. The endothelium over the sites of these changes is frequently intact. When the endothelium has ulcerated there is a thin layer of fibrin on the surface and occasionally this fibrin is collected in verruca-like vegetations (Figure VIII-27).

Histologic appearance of chronic lesions. Healing and repair take place readily. Capillaries surrounded by varying numbers of lymphocytes and mononuclear cells penetrate to the outer half of the endocardium. Fibroblastic proliferation and fibrosis may be present as well as an increase of delicate, distorted elastic fibrils. As healing progresses, the characteristic cells and Aschoff bodies disappear and finally a dense avascular scar is all that is left in the superficial part. In the deeper layers near the myocardium small collections of lymphocytes persist for a long time. Calcium frequently is deposited in the superficial portion of the endocardium where the scar is located. It may appear in thin plates or small nodular clumps.

Other Mural Endocardial Lesions. Aside from the characteristic lesions which appear in the left atrium, the mural endocardium may be involved as an extension of the inflammatory process from the valves, valve rings and chordae tendineae. These lesions are particularly common in the subvalvular angles of the aortic valve, in the septum fibrosum (Gross and Friedberg, 1936) and on the papillary muscles of the left ventricle. Except for these lesions, involvement of the mural endocardium in rheumatic fever is not common. Von Glahn and Pappenheimer (1926) found involvement of the endocardium of the right atrium in only three of 109 cases. In each of these cases the lesion was situated at the margin of the fossa ovalis. In two of them chains of characteristic verrucae were present and in the third a somewhat larger vegetative process was noted.

PERICARDITIS

Incidence. Coombs in 1924 found a progressive decrease in the incidence of pericardial lesions from 100 per cent of patients who had rheumatic carditis and died in the first decade of life to 25 per cent of those who died in the fourth or subsequent decades of life. According to Coombs, the lower incidence in the later age periods indicated that these patients suffered from milder lesions and, therefore, survived longer Friedberg and Gross in 1936 found microscopic evidence of pericarditis in 100 per cent of cases of acute and recurrent rheumatic carditis and in 85 and 75 per cent, respectively, of cases of chronic and healed rheumatic carditis. Clawson (1940a) found pericarditis in 52.5 per cent of the cases of acute rheumatic endocarditis, in 41.1 per cent of cases of recurrent rheumatic endocarditis and in 12.5 to 22.2 per cent of cases in which various types of valvular deformities were present

Acute Pericarditis

Gross Appearance. In gross appearance, acute rheumatic pericarditis differs but little from acute pericarditis of any other type except that the exudate is predominantly fibrinous and rarely serous or frankly purulent (see Chapter IX on Pericarditis) Consequently the amount of fluid in the pericardial sac is likely to be less than in some other varieties of acute pericarditis In cases of early and mild rheumatic pericarditis all that may be seen is a roughening and reddening of the serous surfaces, often limited to one or two patches These early lesions may be observed most readily on the visceral surface of the pericardium particularly at the roots of the vessels and over the atrial appendages In the presence of well-developed pericarditis it may be difficult to open the pericardial sac because it is filled with a thick mat of pinkish fibrin which is firmly adherent to the serous surfaces (Figure VIII-28). A slightly turbid fluid usually oozes from the fibrin, and distinct loculi may be filled with fluid within the fibrin; but it is unusual to find effusion of fluid in rheumatic pericarditis of sufficient quantities to require instrumental evacuation (Coombs, 1924). If the fibrin is removed, the serous surface is found to be rough, reddened and sometimes hemorrhagic. Both pericardial layers are thickened and sometimes this thickening is of a nodular character. The external surface of the parietal pericardium is often bound to the adjacent pleural surfaces by fibrinous adhesions.

Histologic Appearance. The histologic appearance of acute rheumatic pericarditis is similar to that presented by acute inflammation of any serous membrane except for the association of certain lesions which have come to be considered as specific for rheumatic fever (Klinge, 1933) In pericarditis the latter lesions are more frequently overshadowed by the acute inflammatory process than in any other rheumatic lesion. The surface of the pericardium is covered by fibrin in the meshes of which there are usually a few but rarely many leukocytes, including polymorphonuclear leukocytes and occasional histocytes The lining cells on the surface may be intact but more frequently they show evidence of proliferation and, in more severe cases, of desquamation Not infrequently the mesothelial cells desquamate in strips and appear as bizarre pseudoglandular formations (Figure VIII-30*b*) Occasionally the cells proliferate without desquamating and form cystic or solid polypoid structures (Friedberg and Gross, 1934, 1936). In the subepicardial tissue there is usually a diffuse exudate which consists mainly of lymphocytes and plasma cells

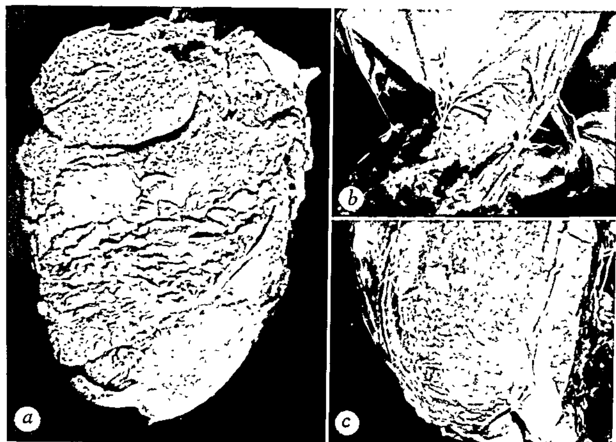


Figure VIII-28 Pericarditis in rheumatic heart disease. *a* Acute fibrinous pericarditis. *b* Chronic adhesive pericarditis *c* Epicardial scar

with an occasional polymorphonuclear leukocyte Vascularization by dilated capillaries is pronounced and even in the early cases there may be beginning organization of the fibrin by fibroblasts and capillaries. Frequently the smaller vessels including the capillaries reveal swelling and proliferation of the endothelium.

In addition to these nonspecific signs of inflammation there are usually foci of fibrinoid degeneration in the connective tissue together with associated collections of the characteristic, large cells with basophilic cytoplasm (Figures VIII-29 and VIII-30) These rheumatic nodules are usually more diffuse and irregular than the corresponding structures in the myocardium. Foci of fibrinoid degeneration of collagen with little or no characteristic cellular reaction may be observed more frequently in the pericardium than in any other site in the heart (Figure VIII-29*a*). Occasionally there is palisading of Aschoff cells and fibroblasts around foci of fibrinoid degeneration or along a necrotic layer of collagen on the surface.

Recurrent Pericarditis

Gross Appearance. This varies considerably with the number and severity of previous attacks of pericardial inflammation and the extent of the recent attack. In all cases a marked thickening of pericardial membranes and an almost universal formation of adhesions are noted. The adhesions tend to obliterate the pericardial cavity. In addition to these evidences of older inflammation there is also fresh exudation of a largely fibrinous exudate. Portions of the older exudate may appear red as a result of extensive vascularization.

Histologic Appearance. In addition to



Figure VIII-29 Pericarditis in rheumatic heart disease

a Fibrinoid change of ground substance Mallory's phosphotungstic acid X 90

b Granuloma in epicardial fat Hematoxylin and eosin X 60

the signs of an older subsiding or healed nonspecific inflammation there is evidence of recent inflammation such as foci of fibrinoid degeneration of the collagen and the associated collections of characteristic cells. These granulomatous foci are often better developed in recurrent than in acute pericarditis Nonspecific signs of recent inflammation in the form of collections of mononuclear and polymorphonuclear cells also may be observed

Chronic and Healed Pericarditis

Gross Appearance. Rheumatic pericarditis may leave as its only mark one or two opaque white patches of thickened epicardium, known as milk spots, or it may leave only a few fibrous tags of no great importance (Figure VIII-28). On the other hand the number and extent of pericardial adhesions may be sufficient to obliterate the entire sac. In addition to these intrapericardial adhesions are the extrapericardial lesions which bind the sac to the mediastinal tissues, lungs and the chest wall. Calcium salts may be deposited in these adhesions and occasionally the heart may be partially surrounded by a solid wall of such depositions. The entity "constrictive pericarditis" sometimes resulting from rheumatic injury is discussed elsewhere (see Chapter IX on Pericarditis)

Histologic Appearance. The thickened walls of the pericardial sac are extensively

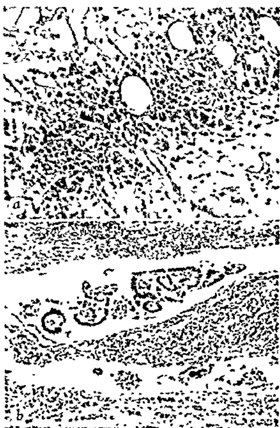


Figure VIII-30 Pericarditis in rheumatic heart disease. Hematoxylin and eosin

a Granuloma in epicardial fat. X 200.

b Pseudoglandular proliferation of epicardial cells X 120.

scarred with a mild inflammatory type of lesion having collections of lymphocytes in the inner layers. Vascularization by thickened vessels and capillaries is often extensive. There is no evidence of fibrinous exudation or other evidence of acute inflammation. The mesothelial lining may be intact or replaced by fibrous adhesions. Deposits of calcium may be observed in the dense connective tissue. For the effects of pericardial adhesions on the myocardium, see Chapter IX on Pericarditis.

LESIONS OF BLOOD VESSELS

Aorta

Involvement of the aorta in rheumatic fever has been recognized and accepted since the systematic histologic study by Klotz in 1912. All portions of the vessel may be involved but the lesions are apparently more numerous in the ascending and thoracic portions (Klotz, 1912, Klinge, 1933). According to Gross (1935a), the aortic and pulmonic roots display a strikingly high incidence of destructive and inflammatory lesions, consisting of scarring, disruption of elastic tissue, vascularization and other inflammatory phenomena. Studies of the incidence of the lesions throughout the aorta have not been made but Klinge stated that involvement of the aorta is the rule rather than the exception.

Gross Appearance. Grossly the lesions have been described as nodular fibrous thickenings by Klotz in 1912; as elevated, almost transparent plaques and ridges of brownish color by Von Glahn and Pappenheimer in 1926, as soft, flat, glassy cushions by Klinge in 1933, and as yellow elevated nodules and streaks by Moore in 1946. In cases of chronic rheumatic disease Klotz noted a great loss in elasticity of the entire wall and the vessel was thicker and heavier.

Histologic Appearance. *Adventitia.* In cases of acute involvement of the adventitia there is congestion of the adventitial vessels with edema and marked infiltration of leukocytes, most of which are lymphocytes. The cellular elements are diffusely scattered throughout the adventitia but tend to be concentrated about the vessels. The foci of fibrinoid degeneration generally are associated with the veins and arteries, which may or may not be involved (Figure VIII-31). They are generally larger and less clearly demarcated than the corresponding lesions in the myocardium (Klinge, 1933). In the granulomatous stage of the inflammatory process the characteristic basophilic cells are found either in the middle or at the borders of the foci of fibrinoid degeneration and giant cells are scarce. In cases of chronic and inactive involvement a nonspecific type of perivascular inflammation may be observed but Aschoff bodies are more difficult to find and may be absent. The adventitia is greatly thickened by collagenous tissue and the walls of the nutrient arteries are thickened.

Media. In the acute stage of rheumatic fever the arterioles are more prominent than usual and penetrate beyond the outer third of the media. Perivascular edema and numerous lymphocytes and plasma cells may be observed. The muscle elements in the neighborhood of the vasa vasorum often have disappeared. Circumscribed rheumatic nodules are not observed but there are foci of fibrinoid degeneration and necrosis which appear in rows. Large basophilic cells are present about the vessels; these also are frequently arranged in rows apparently as a result of the arrangement of elastic fibers. In inactive and healed lesions there is a marked increase in the number and size of the

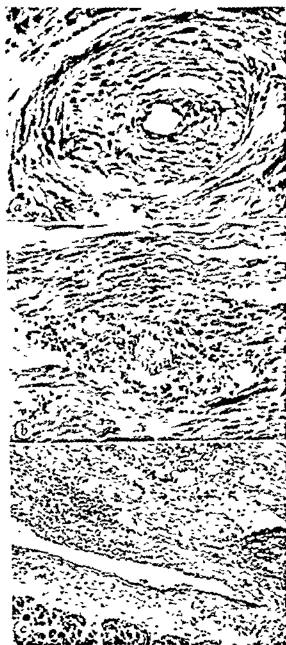


Figure VIII-31 Vascular inflammation in heart disease Hematoxylin and eosin.
a Arteritis showing edema and vacuolization of muscle cells X 290
b Arteritis in granulomatous stage X 150
c Phlebitis with granulomatous inflammation of wall X 115

capillaries, scarring and disruption of elastic fibers. The scars are prominent and have been described as flame-shaped, oval and moth-eaten (Friedberg and Gross, 1936). They are perivascular in distribution and do not involve the entire thickness of the media as in syphilis.

Intima. In this layer lesions are observed which are comparable to those in the atrial endocardium (Von Glahn and Pappenheimer, 1926). There are bands of fibrinoid degeneration of collagen and elastic tissue about which there are large basophilic cells, some of which are multinucleated, and some polymorphonuclear leukocytes. Formation of verrucae is rarely observed In the healed stage the lesion becomes converted into a scar which is difficult if not impossible to differentiate from ordinary aortic sclerosis

Although the intimal lesions frequently occur alone, the adventitial and medial lesions usually occur together It has been postulated, therefore, that the injury to the outer coats comes through the vasa vasorum whereas the intimal injury comes from the blood in the aorta (Klinge, 1933)

According to Von Glahn and Pappenheimer, the rheumatic lesions can be distinguished from those of syphilis in that the former are restricted to the neighborhood of nutrient vessels and are not accompanied by the production of vascular granulation tissue. The cellular constituents are not as numerous; they differ from those observed in syphilitic aortitis and there is no evidence of gummatous necrosis.

Coronary Arteries

In this section involvement of the adventitia of the smaller branches, which is a site of predilection for the myocardial rheumatic nodule, will not be considered, but involvement of the media and intima of the larger branches will be considered particularly In these vessels inflammation of varying degree occurs in about one-third of the active cases of rheumatic fever. The lesions of rheumatic fever in these vessels consist of edema, exudative and necrotizing inflammatory changes, fibri-

noid degeneration, palisade formation, verrucous endarteritis and thrombi (Gross, Kugel and Epstein, 1935). Except when Aschoff bodies are a part of the inflammatory process the lesions are not specific for rheumatic fever. Destruction of elastic fibers seems to be especially severe. According to Klinge, the fibrinoid degeneration of the ground substance and the lymphocytic and leukocytic exudation often are more pronounced than the proliferation and hypertrophy of the connective tissue cells. Also according to him, longitudinal sections of the coronary arteries reveal a palisade arrangement of cells of the wall, such as has been described in the atrial and aortic lesions. Fibrosis of the coronary arteries occurs more frequently, more extensively and considerably earlier than in nonrheumatic control cases. Although these changes have not been shown to result from acute inflammatory lesions, it is practically certain that severe myocardial injury is associated with the disease in the coronary arteries (Karsner and Bayless, 1934)

Other Vessels

Lesions of small peripheral arterioles and capillaries occur in various locations including the lungs (Von Glahn and Pappenheimer, 1926; Paul, 1928). Sloughing of the endothelium as a result of exudation of fibrin into the wall, necrosis of the cellular constituents and fragmentation of the elastic lamellae have been described. In the perivascular tissue there is an exudate consisting of polymorphonuclear cells, radially arranged mononuclear cells and an outer loose infiltration of lymphoid and plasma cells and occasional eosinophils and fibroblasts. In this perivascular tissue are many dilated hyperemic capillaries which may extend far beyond the area of cellular infiltration. Thrombosis is not observed in these vessels. The acute lesions are followed by organization with or without formation of new collateral channels within the thickened intima and occasionally within the muscular layer. The lesions resemble most closely those of periarteritis nodosa but differ from these in the absence of thrombosis, the small size of the involved vessels, and the absence of nodules or aneurysmal formations. Identical changes have been described in pulmonary arterioles by Von Glahn and Pappenheimer as well as by Paul. Rheumatic lesions in the veins occur (Figure VIII-31*c*) and have been studied extensively by Klinge (1933).

Relation to Other Similar Vascular Disease

As Karsner and Bayliss (1934) have pointed out, it is difficult to orient the vascular lesion of rheumatic fever in the whole group of arterial diseases. Aschoff (1906), Ophuls (1923), Friedberg and Gross (1934), Neale and Whitfield (1934) and Middleton and McCarter (1935) have stressed the close relationship between periarteritis nodosa and rheumatic fever. Friedberg and Gross, in particular, were of the opinion that rheumatic fever was a common cause of the vascular lesion termed "periarteritis nodosa." Fahr in 1920 suggested that rheumatic arterial disease may be a causative factor in malignant sclerosis and in 1921 drew attention to the resemblance between the arterial lesions of rheumatic fever, polyarteritis nodosa and dermatomyositis. Klinge (1933) and Vaubel (1932) considered periarteritis nodosa, malignant sclerosis, certain forms of cardiovascular sepsis, thromboangiitis obliterans, focal glomerulonephritis and rheumatic fever in the same group on the basis of hyperergic causes. Semsroth and Koch (1930) as well as Metz (1931) were of the opinion that the arterial lesions of acute infectious disease, rheumatic fever and polyarteritis nodosa, are manifestations of the allergic state which differ only

in degree of involvement. It is interesting in this connection that methods capable of producing lesions resembling periarteritis nodosa in animals also produce lesions simulating those of rheumatic fever (Rich and Gregory, 1943; Selye, 1946, 1947). It is obvious that more work along this line of investigation is necessary before a final conclusion can be reached concerning the relation of rheumatic vascular lesions to those of periarteritis nodosa.

RHEUMATIC LESIONS IN DISEASES OTHER THAN RHEUMATIC FEVER

The occurrence of nodules in cases of subacute bacterial endocarditis similar to or identical with those observed in cases of rheumatic fever is mentioned in the section on Endocarditis The occurrence of lesions in cases of scarlet fever similar to those of rheumatic fever has been commented on in the discussion of the specificity of the Aschoff body. The occurrence of rheumatic-like lesions in syphilitic aortitis reported by Clawson (1929) need not be considered further because the demonstration of the etiologic agent and the other characteristic features of the latter disease usually are sufficient so that the differential diagnosis can be made without difficulty. The rare occurrence of rheumatic-like lesions in meningococcic endocarditis (Rhoads, 1927) or typhoid fever (Romberg, 1894) likewise offers no serious problems The occurrence of rheumatic lesions in cases of rheumatoid arthritis, however, has aroused considerable interest because of the long-standing problem concerning the possible relationship of the two diseases.

Cardiac Lesions Associated with Rheumatoid Arthritis

Opinions as to the presence and nature of cardiac lesions associated with rheumatoid arthritis have varied According to the older clinical reports, the incidence of cardiac lesions varied from four (Coates, 1931, Monroe, 1936) to 40 per cent (Kahlmeter, 1934) The value of these clinical reports is limited because. (1) The type of chronic arthritis studied is not always clearly defined, (2) clinical data are often insufficient so that accurate diagnosis of the nature or site of a cardiac lesion cannot be made, and (3) mild or healed cardiac lesions may give no clinical indication whatsoever of their presence.

Studies of the pathologic changes in the heart in cases in which chronic infectious arthritis is known to have occurred during the life of the patient were made by Charcot (1881), Kast (1901) and Grzimek (1932). These studies, however, are difficult to interpret because the type of arthritis is not clearly defined. Baggenstoss and Rosenberg (1941, 1943, 1944) and Rosenberg, Baggenstoss and Hench (1944) have reported the results of studies at the Mayo Clinic in which both the criteria used for the diagnosis of rheumatoid arthritis and the character of the cardiac lesions were carefully described. Cardiac lesions indistinguishable from those produced by rheumatic fever were found at necropsy in 16 (53 per cent) of 30 cases. Since these reports were published, 14 additional cases have been studied at necropsy (Baggenstoss and Englund, 1950) in five of which (36 per cent) similar cardiac lesions were found. Three possible explanations were considered for the unexpected high incidence of rheumatic heart disease in cases of rheumatoid arthritis. The first was that by chance a series of cases had been studied in which an indep

rheumatic heart disease was unusually common If this explanation is correct, the findings in these cases actually do not reflect accurately the true incidence of the two conditions in the same cases. The second possibility considered was that the "rheumatic" cardiac lesions were not caused by rheumatic fever, but represented a similar disease caused by the agent responsible for rheumatoid arthritis If this is correct, a heretofore unrecognized condition, rheumatoid heart disease, was observed. A third possible explanation was that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis even in the absence of a history of frank attacks of rheumatic fever.

The first of these explanations appears least likely to prove correct because the cases constituting the series were chosen without regard for the presence or absence of heart disease The presence of rheumatic heart disease, however, might increase he chance that death would occur while the patient was at the Mayo Clinic. Thus the factor of selection would enter into the high incidence of rheumatic heart disease

The possibility that rheumatoid arthritis may be associated with inflammatory cardiac lesions similar in appearance to, but of different cause from, rheumatic fever cannot be lightly dismissed. Nevertheless the lesions which were designated as those of rheumatic heart disease would be so diagnosed by most American pathologists. The late Dr H. E. Robertson reviewed the cardiac lesions and concurred in the diagnosis of rheumatic heart disease. Dr. B. J. Clawson of the University of Minnesota has likewise stated that these lesions represented rheumatic heart disease. It is interesting in this connection that in two cases cardiac lesions were observed which histologically were strikingly similar to the subcutaneous nodules of rheumatoid arthritis. These unusual cardiac lesions have been discussed in greater detail in another report (Baggenstoss and Rosenberg, 1944). They differed from typical rheumatic lesions of the heart in that they were much larger and there was much more necrosis in the central portion. Similar lesions have since been described by Raven, Weber and Price (1948). Bennett in 1943 observed three patients who had rheumatoid arthritis and succumbed to heart disease of unknown cause. The cardiac lesions were not described but he hoped that further study of these and similar cases might aid in ascertaining whether the heart changes represent an unusual manifestation of rheumatoid arthritis, are related in some manner to rheumatic fever or are associated with coincidental disease. Wallis in 1948 suggested that the relationship between rheumatic fever and rheumatoid arthritis is based on a similar pathogenesis (hypersensitivity, antigen-antibody reaction) but a different cause.

The possibility that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis even in the absence of a history of frank attacks of rheumatic fever has received considerable support from the recent clinical studies of Dawson (1943); Ellman (1944); Feiring (1945), Coss and Boots (1946); Pickard (1947), and Fischmann and Gwynne (1948) The pathologic studies of Baggenstoss and Rosenberg have been confirmed by Smyth (1943), Fingerman and Andrus (1943), Bayles (1943); Young and Schwedel (1944); and in these reports the incidence of rheumatic heart disease in cases of rheumatoid arthritis varied from 26 per cent (Bayles, 1943) to 65.7 per cent (Young and Schwedel). The accumulating evidence of the high coincidence of the two conditions is becoming more and more impressive and suggests even more strongly that rheumatoid arthritis and

rheumatic fever are in some manner closely related conditions. The nature of this relationship is not clear and probably will not be understood until after the discovery of the etiologic agent or agents of these diseases. It may be noted that both rheumatic fever and rheumatoid arthritis respond favorably to daily intramuscular injections of certain hormones of the adrenal cortex and the pituitary gland (Hench *et al.*, 1949).

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CHAPTER IX

Nonrheumatic Inflammatory Diseases of the Heart

A. Pericarditis

OTTO SAPHIR

A NORMAL PERICARDIUM, like other normal serous membranes, is smooth, glistening and transparent. It is glistening because it is covered by a single layer of mesothelial cells; smooth because the cells are similar over the entire pericardium and are not covered by any foreign material, transparent because there is no other substance between the mesothelium and the underlying subepicardial fatty tissue and myocardium. Any deviation from these three characteristics must be considered abnormal. In instances of acute inflammation, when the epicardium is covered with fibrin, it appears dull because of the presence of the exudate over the mesothelial cells, rough because of the irregular distribution of the exudate, and opaque because the underlying tissue is not visible. If the fibrin deposits are recent, they can be scraped away easily and the pericardium will again appear smooth, glistening and transparent. If the epicardium is smooth and glistening but opaque, so that the underlying subepicardial fatty tissue cannot be viewed, there is newly formed connective tissue between the epicardium and myocardium. Such newly formed connective tissue indicates, most commonly, scar tissue and one is thus justified in making a diagnosis of a healed (circumscribed) pericarditis.

Fluids in Pericardial Sac

The pericardial sac normally contains, according to Karsner (1949), about 20 to 50 ml. of clear yellow liquid, while Kaufmann (1922) stated that the amount of fluid normally present is from 5 to [illegible] and Hall (1948), from 5 to 50 ml. In my experience, the figures that Karsner gives seem more appropriate. An increased amount of fluid indicates either a transudate or an exudate. Larger amounts of fibrin are always characteristic of an exudate while transudates contain a small amount of fibrin.

Hydropericardium [illegible] is most often one of the [illegible] of generalized chronic pa[illegible] it may be part of [illegible]. [illegible] the fluid is exces[illegible]

actually to compress the veins which open into the atria. In such an event, there is a decrease in the arterial pressure and an increase in venous pressure. The systemic pressure may be sustained for a considerable period of time by vasoconstriction. As has been shown, increased intrapericardial pressure may affect the heart muscle and its rhythm by a relative anoxemia of the myocardium. Alteration of the normal variations of intrapericardial pressure, due to excessive pericardial fluid, may cause pulsus paradoxus. An interesting condition sometimes observed in old people is the occurrence of hydropericardium as the *only manifestation of chronic* passive hyperemia of serous cavities. Since, in such instances, the heart often is atrophic, the older pathologists coined the term *hydrops ex vacuo*. Large quantities of pericardial fluid, one to two liters, often cause surprisingly little disturbances (Hall). If, however, the pericardium is thickened as a result of previous inflammation, small quantities of fluid may produce tamponade.

Hemopericardium. The presence of blood in the pericardial sac may be the result of penetrating wounds of the heart, rupture of an aneurysm of the ascending aorta or of the arch of the aorta, rupture of a recent myocardial infarct, or of mycotic erosive myocardial aneurysms (see page 714). A hemorrhagic exudate is the result of tuberculosis, a number of other infections, such as anthrax, of primary or metastatic tumors, or of diseases having a hemorrhagic tendency.

Pneumopericardium is a rare condition. It may be the result of mechanical trauma, of perforation of a carcinoma of the esophagus or bronchus into the pericardium, or it may occur as a complication of a pyopneumothorax. Rarely gas-forming organisms may produce pneumopericardium, and in such an instance the term *pneumatosis pericardii* may be used.



Figure IX-1. Healed pericarditis with large "soldier spots."

Milk Spots

The most common abnormalities of the pericardium are the so-called pericardial *milk spots* (Figure IX-1). Other terms are "soldier's spots," "tendinous patches" and "maculae tendineae." They were described as early as 1806 and since that time their origin has been disputed (Nelson, 1940). The old explanation for these spots was mechanical trauma. It was thought that pressure of the sternum upon the ventral wall of the right ventricle, where these patches are most commonly located, produces a chronic irritation and a resultant chronic inflammation with new formation of connective tissue between the epicardium and myocardium. Since it was thought that the straps of knapsacks carried by soldiers may produce such chronic irritation upon the visceral pericardium, such patches were named "soldier's spots." Multiple patches are somewhat more frequent than single ones. Most commonly they are from 1 and 3 cm. in greatest diameter. The right side of the heart is much more commonly involved than the left side.

Nelson, who studied 494 hearts of patients one year old and over, found 170 (34.4 per cent) with one or more pericar-

dial milk spots. Of 439 persons 18 years old and over, the hearts of 165 (37.6 per cent) showed such milk spots. Nelson concluded that there should be a definite and marked increase of incidence with age if the production of milk spots were on a purely mechanical or age basis. However, such an increase could not be demonstrated.

Microscopically, milk spots are characterized by a new formation of connective tissue which is covered by normal-appearing mesothelial cells. The connective tissue is loose, and often small or larger collections of lymphoid cells are observed. Occasionally small foci of mesothelial cells forming pseudo-glandular or canalicular formation, of the type to be discussed subsequently, are noted within the loose connective tissue.

It seems evident that these milk spots are the result of *old circumscribed pericarditis*. Nelson remarked on their association with chronic or recurrent valvular heart disease. In his series, patients with severe coronary arteriosclerosis and enlarged hearts also had a fairly definite increase in the size and number of milk spots It also may be mentioned that in 20 per cent of spots examined, Nelson's findings suggested transitions from a more active inflammatory process to the usual type of spot

Acute Pericarditis

The *gross picture* of acute serofibrinous pericarditis is characteristic. Early lesions are particularly well seen on the visceral pericardium (epicardium). The epicardium has lost its gloss and has a deposition of fibrin which produces a fine, granular appearance of the epicardium. In this stage the pericardium looks like velvet. Sometimes when inspected with a magnifying glass, the fibrin is seen in the form of a minute network which may be scraped away easily with a scalpel. Such very early fibrinous pericarditis is often noted in the region of the pericardium covering the great vessels. This is probably because of the great number of vasa vasorum in the region of the reduplication of the pericardium covering the great vessels. Later, when more fibrin is deposited, the netlike arrangement of the fibrin is no longer recognized. The fibrin becomes arranged in *smaller and larger clumps*, *is nodular* and distributed throughout the parietal and visceral pericardium. Still later, the fibrin appears in the form of characteristic villi, in more or less isolated masses, while the remainder of the pericardium may be more diffusely covered with fibrin. This is the so-called "bread and butter exudate" or the *cor villosum*, the latter term indicating the resemblance to sheep's fur In addition to the deposit of fibrin, some pus is usually present In instances in which the amount of fluid is minimal, the term *pericarditis sicca* is used. However, in those instances in which initially both fibrin and serum are present, serum alone may be absorbed and thus *pericarditis sicca* may result According to Ribbert (1897), Monckeberg explains the formation of villi as follows: During diastole the epicardium is well expanded but during systole it becomes relaxed and wrinkled When fibrin is formed, it is deposited principally within the base of the wrinkles; thereafter, additional fibrin becomes adherent to older fibrin and thus the so-called villi are formed.

Microscopically, acute pericarditis is similar to inflammation of other serous membranes The pericardium is covered by fibrin with many enmeshed polymorphonuclear leukocytes, a few lymphocytes and occasional histiocytes. The subepicardial layer contains dilated capillaries. Some lining mesothelial cells may become desquamated, whereas others are swollen or show fatty degeneration. In instances of purulent pericarditis, polymorphonuclear leukocytes are abundant and many of them

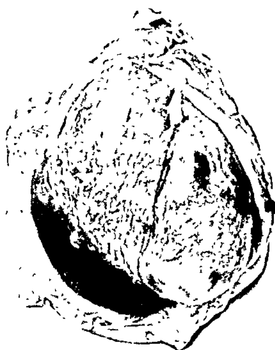


Figure IX-2 Uremic pericarditis. Fibrinous exudate. (WCGH, 40 A 265)

show degenerative changes. In severe pericarditis the superficial layers of the myocardium also are often involved.

In *uremic pericarditis* most of the exudate consists principally of fibrin (Figure IX-2) Only a few polymorphonuclear leukocytes are present (Herzog and Marchand, 1921b) Pericarditis, or perhaps it would be better to say an excessive amount of pericardial fluid, is often found in *myxedema* Schnitzer and Gutmann (1946) stated that the similarity of the electrocardiograms in cases of pericardial effusion and in cases of myxedema suggests a common abnormality, which may be the presence of excessive fluid in both of these disorders. This would, they remarked, support the opinion that a pericardial effusion exists in many if not in all cases described as "myxedema heart."

Often, acute fibrinous pericarditis may heal with complete restitution. The lining mesothelial cells regenerate and the inflammatory exudate is absorbed. In other instances the acute inflammatory exudate becomes organized and is eventually replaced by granulation tissue and scar tissue. Such scars may be confined to one of the layers of the pericardium. Since they are completely covered by regenerated mesothelial cells, they appear smooth and glistening but opaque. In those instances in which the fibrin extends from the visceral to the parietal layer of the pericardium, newly-formed blood vessels and eventually young fibroblasts and connective tissue fibers will extend from one layer of the *pericardium through the fibrin masses to* the opposite layer. Thus, the organized fibrin is essential for the production of adhesions between the visceral and parietal pericardium. Gradually granulation tissue extending from both the visceral and parietal pericardium traverses the exudate The entire pericardial cavity may become completely obliterated by adhesions to produce an *adhesive pericarditis with obliteration of the pericardial cavity.* The term *synechia cordis* is also sometimes used to indicate adhesions between the two layers of the pericardium

The behavior of the lining mesothelial cells in healed or adhesive pericarditis is interesting. It often happens that regeneration of these cells occurs at the base of the normal epicardial wrinkles. When, because of the organization of the exudate, the wrinkles or crevices are bridged over by connective tissue, regenerated mesothelial cells also grow on the inner surfaces of these connective tissue bridges and line the spaces thus created. On microscopic section, therefore, many thin spaces lined by mesothelial cells may be found within the scar tissue close to the pericardial surface (Ribbert, 1897). Since these lining mesothelial cells are often somewhat swollen, these spaces resemble glandular or adenomatous structures (Figure IX-3). Rarely, these may give rise to droplike cysts covering the pericardium (Lauche, 1919).

In instances of healing of acute pericarditis when the inflammation also involves the external surfaces of the parietal pericardium (external pericarditis), resulting adhesions may involve the mediastinum and adjacent structures, such as pleura, lungs and intercostal muscles The term *mediastinopericarditis* is used in such cases

Incidence of Pericarditis

Wells (1902) found 128 instances of pericarditis among 1048 autopsies. Fifty-seven were classified as acute and 71 as chronic. Locke (1916) found acute pericarditis 150 times and chronic pericarditis 209 times among 3683 autopsies Eighty-eight hearts disclosed milk or soldier's spots. Among 118 instances of acute pericarditis, 42 were classified as acute fibrinous, 33, acute serofibrinous, 4, hemorrhagic; and 39, purulent. Musser and Herrmann (1926) found either acute or chronic pericarditis in 11 9 per cent of 1720 autopsies. Smith and Willius (1932) reported 373 instances of pericarditis among 8912 cases. One hundred and forty-four of these were classified as adherent pericarditis It is interesting that these authors also commented upon a distinct predominance of males in the statistics of acute pericarditis



Figure IX-3 Organized pericarditis Note pseudoglandular spaces lined by mesothelium Hematoxylin and eosin. X 150.

Causes of Pericarditis

Pericarditis is usually the result of invasion of the pericardium by bacteria. Exceptions to this general rule are instances of pericarditis associated with rheumatic fever, myocardial infarcts, kidney lesions (uremic pericarditis), and tumors. Bacteria may enter the pericardium as a result of a perforating trauma and of inflammations of neighboring organs or structures. In such cases it is not always necessary to demonstrate the actual extension of the inflammation from the pleura (Figure IX-4) or lymph node or anterior mediastinum into the pericardium, but bacteria may find their way to the pericardium by lymphatic spread or "migration," as has been pointed out in instances of peritonitis (Wile and Saphir, 1932). Pericarditis is not a rare complication of myocarditis. On the other hand, pericarditis may also lead to myocarditis. Only rarely may one demonstrate the actual extension into the pericardial sac of an abscess of a lymph node, or of a myocardial or pulmonary abscess, or of a pleural empyema Zodikoff (1947) recorded an instance of multiple abscesses in the liver with rupture into the pericardial sac Smith and Willius (1932) pointed out that pericarditis in their series of 373 cases was associated with the following conditions, in the order given (1) rheumatic fever, (2) intrathoracic infection, (3) cardiac infarction, (4) syphilis (its etiologic role, however, was doubtful), and (5) neoplastic invasion.

Pericarditis associated with rheumatic fever, acute bacterial endocarditis and endocarditis lenta will be discussed elsewhere.

Pericarditis is not rarely a complication of pyemias In such instances the question is often raised whether the pericardium becomes infected directly by bacteria circulating in the blood stream (*primary pericarditis*) or whether the organisms produce



Figure IX-4 Fibrinopurulent pericarditis secondary to empyema of pleural cavity. From a man of 46 (WCGH, 44 A 412.)

a small abscess adjacent to the pericardium with perforation of the abscess and resulting *secondary pericarditis.* From studies of the etiology of tuberculous meningitis (Rich and McCordock, 1933) and from personal experience, the latter mechanism seems much more likely. Careful gross and microscopic studies will almost always disclose a small or minute abscess, most commonly located within the adjacent myocardium or other adjacent structures with secondary pericarditis. (See also Wile and *Saphir [1932] for their discussion of* so-called primary peritonitis.) Perhaps the only exception to this general rule is the acute pericarditis found in instances of acute rheumatic infections. However, since the myocardium is so often involved in this disease, the pericardium may be the result of the rheumatic myocarditis. Among 113 cases of pericarditis with effusion (Smith and Willius, 1932), only three were non-inflammatory and three of tuberculous origin; the remainder were classified as acute purulent and acute fibrinous pericarditis with effusion. Intrathoracic infectious diseases occurred with greatest frequency. As a matter of fact, these authors stated that it appears to be established that the presence of infectious intrathoracic disease offers a great chance for involvement of the pericardium, and in infectious processes of the body as a whole, the chances of development of pericarditis are even greater. Thus, the presence of infection should always focus attention on the peri-

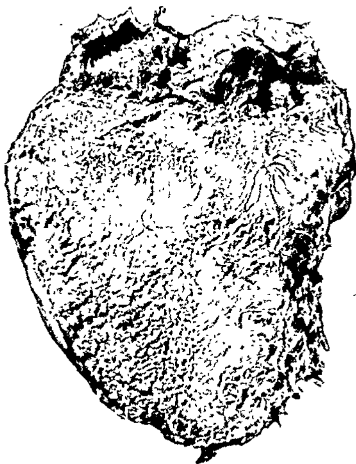


Figure IX-5 Acute fibrinopurulent pericarditis secondary to empyema of pleural cavity. Pericardial cavity contained approximately 1000 ml. of fluid From a man of 70 (WCGH, 40 A 132)

cardium, so that purulent pericarditis (Figure IX-5) or fibrinous pericarditis with effusion may be recognized more commonly. In myocardial infarcts, if the necrosis is close to the pericardium, serofibrinous pericarditis may result. This is interpreted as an example of a "sterile" inflammation, the dead muscle fibers causing a nonspecific reaction not only of the surrounding interstitial tissue, but also of the pericardium Inasmuch as numerous polymorphonuclear leukocytes surround and infiltrate infarcted muscle fibers, usually large numbers of polymorphonuclear leukocytes are also present in such a pericarditis. It is noteworthy that such a pericarditis is not necessarily confined to the portion of the pericardium adjacent to the infarct, but may be diffuse.

Uremic pericarditis, usually classified as chemical pericarditis, is characterized by the rarity of polymorphonuclear leukocytes. Its mechanism is not known.

Virus Pericarditis. There are no recent studies available concerning the occurrence of pericarditis caused by viruses. Since pericarditis may result from an extension of a myocarditis, and since myocarditis occurs in virus infections, pericarditis may be presumed to be present in virus infections.

Thus Monckeberg (1924) mentioned in-



Figure IX-6 Tuberculous pericarditis. From a 66-year-old man. (WCGH, 45 A 265)

stances of pericarditis in measles and smallpox Interesting is a report by Herzog and Marchand (1921a) of pericarditis as a complication of epidemic encephalitis. They remarked that the pericarditic exudate consisted almost entirely of lymphocytes.

Tuberculous Pericarditis. In disseminated miliary tuberculosis, tubercles may be found in the pericardium. Karsner (1949) has pointed out that, while the pericardium that is the seat of miliary tubercles often has little or no inflammation, in tuberculous pericarditis the inflammation is marked, whether it is acute or chronic. At autopsy the pericarditis is usually chronic, with extensive adhesions of both layers of the pericardium, remnants of fibrin and much caseation (Figure IX-6). Conglomerate tubercles (Figure IX-7) also are often present. The exudate is usually fibrinous in type with varying amounts of hemorrhages.

Harvey and Whitehill (1937) studied 95 instances of tuberculosis of the pericardium. Pericardial fluid was examined during life in 13. In two of these cases, acid-fast bacilli were found in smears of the sediment, and in one case, the organism was cultured; in five cases, tubercle bacilli were proved to be present by guinea pig inoculation. In seven of the 13 cases, therefore, the diagnosis was supported by smear or proved after guinea pig inoculation. In 12 instances a considerable amount of fl[illegible]

sac. [illegible] varied in quantity from 150 to 1350 ml. The pericardial cavity was always enlarged.

The description of the above authors is quite fitting in most instances of tuberculous pericarditis. The parietal pericardium

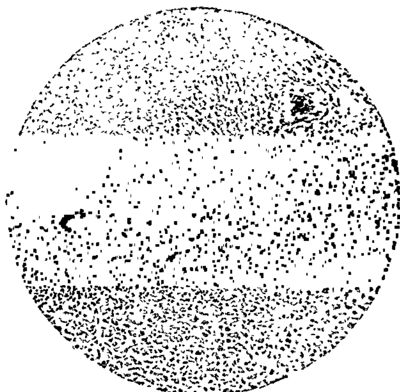


Figure IX-7 Tuberculous pericarditis From same case as Figure IX-6 Hematoxylin and eosin. X 265

is thickened and leathery, and often nodular tubercles are visible from without Thick, fibrous, organizing adhesions are *sometimes* noted with adhesions of the pericardium to lungs, diaphragm and sternum The visceral layer is usually covered by a mass of thick, shaggy, flaky, reddish fibrin, often assuming a corrugated appearance Below the superficial layer of fibrin, there is a zone of granulation tissue. On section many circumscribed, minute, yellow, opaque areas are scattered throughout. Sometimes tuberculous lymph nodes are present adjacent to the pericardium Most frequently the peribronchial, peritracheal and mediastinal nodes are involved, and less commonly the periaortic and anterior mediastinal nodes Often the pericardial sac is obliterated by fibrous tissue Also on the parietal pericardium hard, yellowish nodules are often seen with necrotic centers

In one instance Harvey and Whitehill (1937) thought that the tuberculous pericarditis was primary, since at autopsy the mediastinal nodes were normal, the lungs showed no abnormalities, and no other tuberculous lesions were found

Syphilis of Pericardium. *Gummas* of the pericardium have been reported in the older literature (see Monckeberg, 1924). They are extremely rare. The occurrence of syphilitic pericarditis is questionable Stockmann (1904) who had collected from the literature 79 instances of gummas in the myocardium, found that 10 of these also disclosed pericardial lesions. Six of these 10 showed either complete or partial adhesions of both layers of the pericardium.

Other Infections. Cornell and Shookhoff (1944) collected 65 instances of *actinomycosis* of the heart and mentioned involvement of the pericardium. *Amebic*

pericarditis had been described 22 times according to Kern (1945), though pericardial involvement in the course of amebic abscesses of the liver has been reported more frequently. Kern studied an instance of amebic pericarditis subsequent to extension of an amebic abscess of the liver. *Endamoeba histolytica* was demonstrated in the pericardium. The clinical impression had been tuberculous pericarditis. D'Mello (1947) reported perforation into the pericardial sac of a large amebic abscess of the liver, with the production of pericarditis and the finding of amebæ in the pericardial cavity (See page 837.)

Adherent Pericardium. Adhesions between the parietal and visceral layers of the pericardium may represent either chronic pericarditis or the end stage of acute pericarditis, — scars or healed pericarditis. The chronicity of the inflammation must be proved microscopically, *i e.*, there must be evidence that active inflammation is still present and has not come to a standstill. True chronic adhesive pericarditis is common in rheumatic fever and in tuberculosis As has been mentioned before, as a result of adhesions between the two layers of the pericardial sac, the pericardial cavity may be partially or completely obliterated, and the term *synechia cordis* is used for this condition. The older pathologists spoke of "concretio cordis." The connective tissue forming these adhesions often becomes hyalinized and sometimes calcified This is especially true of old tuberculous pericarditis. Well-marked calcification of portions of the pericardium occurred in 15 of the 144 cases of adherent pericarditis reported by Smith and Willius (1932) and in four of Wells' (1902) series. Wells pointed out that synechia cordis may be present without any effect upon the patient.

Mediastinopericarditis refers to the condition in which fibrous tissue binds the heart firmly to the adjacent tissues, including the rigid structures, ribs and their cartilages, sternum and vertebral column. In the older terminology this was called *accretio cordis*. The firm attachments of the heart to the neighboring structures frequently result in retraction of the precordial interspaces with each contraction of the heart. This is regarded by most observers as an added burden on the heart, and it may be a factor in the cardiac enlargement and heart failure which occur not infrequently in these patients. Laws and Levine (1933) found that the average heart weight of patients with mediastinopericarditis and valvular disease is greater than that of patients with valvular disease only. In their patients, the average weight of hearts with valvular disease and mediastinopericarditis was 654 grams, while the average weight of hearts with valvular disease but without pericarditis was 534 grams. This is interpreted as meaning that external adhesions increase the work of the heart However, there are also a number of investigators who doubt that hypertrophy is the direct result of overwork of the heart because of the adhesions. Hypertrophy which is often encountered in such hearts is explained on the basis of valvular lesions which also are often present It must be pointed out that the weight of the heart, in instances of old pericarditis with adhesions (of constrictive pericarditis and mediastinopericarditis) is extremely difficult to determine. The weights which are usually given consist of the combined weight of the heart and the adhesions, and it is difficult to judge the degree of hypertrophy. Usually, when old valvular diseases are found, the hypertrophy of the heart is believed to be the result of these valvular changes. Thus, in one case, Mallory (1947) stated that the heart and the pericardium together weighed 450 grams and the heart was actually small, its estimated weight being about 250 or 275 grams. Mediastinoperi-

carditis may be caused by rheumatic fever and by tuberculosis, or may be a complication of purulent pericarditis.

Constrictive pericarditis. Sometimes, as the result of healing of purulent or tuberculous pericarditis, dense and thick adhesions are formed, the layers of the pericardium may become rigid and actually cause limitation of the diastolic expansion of the heart (Wells, 1902). The term *constrictive pericarditis* applies to such instances. The outstanding physiologic effect in such patients is the reduced inflow of blood to the heart This is recognized clinically by dyspnea on exertion, cyanosis and ascites, and by increased venous pressure and low pulse pressure. Blalock and Burwell (1941) defined *chronic constrictive pericarditis* as a thickening and contraction of the pericardium or epicardium or both, to such an extent that there is interference with the normal action of the heart. The pericardial sac may be completely obliterated or there may be areas in which the two layers are not adherent. The pericardium may or may not exhibit areas of calcification, usually it does not. Small collections of fluid may be trapped between the thickened epicardium and pericardium. Associated disease of the heart itself is rare except for atrophy of the myocardium in advanced cases. There are a number of reports in the literature of such a condition being recognized clinically, in which operation was performed with the view of cutting the adhesions Many such operations have been successful (see Beck, 1931, Blalock and Burwell, 1941) From the foregoing it can also be surmised that mediastinopericarditis occasionally may lead to inflow disturbances of the heart, particularly if the region of entrance of the inferior vena cava into the right atrium is involved. This type of mediastinopericarditis is also referred to as *constrictive pericarditis*

It is sometimes stated that constrictive pericarditis is caused by rheumatic fever. However, Harrison and White (1942) are certain that rheumatic fever is rarely, if ever, an etiologic factor.

Pick, as early as 1896, concluded that a complex of symptoms similar to that produced by primary cirrhosis of the liver could be caused by an old but clinically latent fibrous pericarditis. As a result of the pericarditis, circulatory disturbances of the liver ensue with stasis in the portal circulation and proliferation of connective tissue within the liver, and finally severe ascites. He used the term "pericarditic pseudocirrhosis of the liver." He also emphasized that the syndrome of Curschmann, characterized by severe ascites and perihepatitis, was the result of an old pericarditis. Curschmann (1884) had pointed out that primary perihepatitis (frosted liver, hyalocapsulitis) may be so severe as to cause encroachment upon the liver parenchyma and the branches of the portal vein by the newly-formed contracting connective tissue and thus produce severe ascites. However, it was pointed out a few years later by Pick that Curschmann's patient also had an old pericarditis and Pick, therefore, thought that the ascites and perihepatitis were the result of the old pericarditis Eisenmenger, in 1900, admitted that severe ascites may occur in instances of adhesive pericarditis in the absence of edema of the lower extremities However, he thought that the ascites was not the result of vascular disturbances within the liver itself with consequent fibrosis, but that it was caused by several factors, primarily by compression or angulation of the inferior vena cava or perhaps by a localized peritonitis at the hilus of the liver. Therefore, he condemned the term "pericarditic pseudocirrhosis of the liver," because this terminology would embrace only a single etiologic factor. Mönckeberg (1924) advocated the term "Pick's disease" for those instances in which adhesive pericarditis, adhesive pleuritis and

hyalocapsulitis (Zuckerguss, cake-icing) of the liver, are present It is imperative in such instances to examine carefully the inferior vena cava at its entrance into the right atrium Because of mediastinopericarditis, this portion of the inferior vena cava may become narrowed and lead to severe distention of the hepatic veins and ascites. In this connection it may be mentioned that Monckeberg also described a type of old pericarditis without adhesions, but with marked fibrosis of both layers of the pericardium; also with nodules consisting of completely organized fibrin covered by mesothelium Both layers of the pericardium may then have thick, white, smooth or nodular surfaces, and the term "frosted" pericardium (Zuckergussherz) may be applied Kaufmann (1922) pointed out that such a "frosted" pericardium in particular may give rise to Pick's syndrome with hyalocapsulitis of liver and spleen (Zuckergussleber and Zuckergussmilz). White (1944) stated that Pick's disease may or may not be associated with polyserositis (Concato's disease)

Occasionally, as a result of an adhesive pericarditis, granulation tissue and resulting scar tissue cause narrowing of the inferior vena cava at the site of its entrance into the right atrium. This constriction is situated just above the site of opening of the hepatic veins into the vena cava. Apparently, because of the angle which is formed by the vena cava and the hepatic veins, there is a damming back of blood into the liver. The circulation of the vena cava below this level is relatively not impeded. The openings of the hepatic veins into the inferior vena cava, however, are greatly dilated and as a result, the liver develops a *diffuse periportal fibrosis* but not a true cirrhosis. Ascites then appears but is not accompanied by edema of the lower extremities. In a patient observed by us, the ascites was early and persistent, but there was no edema of the lower extremities It is evident that these changes will be much more severe if complicated by old endocarditis of the tricuspid valve, since insufficiency of this valve increases the resistance of inflow into the right atrium. This type of pericarditis is really a mediastinopericarditis

Pericarditis with much cholesterol within the inflammatory exudate was described first by Daniel and Puder (1932), and later by Merrill (1938) It was suggested by the former authors that the cholesterol was a secondary deposit in certain instances of tuberculous pericarditis with hemorrhage into the pericardial sac. From the description, however, it seems possible to explain the presence of cholesterol as a result of a coincidental fat necrosis occurring within the subepicardial fat tissue.

Calcification of the Pericardium is occasionally observed as the end result of an old pericarditis. It is found relatively often *in association with tuberculous pericarditis* Among Smith and Willius' (1932) 144 cases of chronic adherent pericarditis, there were 15 disclosing calcification The extent of calcification varied from a few areas to involvement of the entire pericardium with the exception of a small portion of the apex This extreme degree of involvement, however, was present only in one case. These authors also stated that the single etiologic factor which affected the largest number of patients was a supposed rheumatic infection. In Harrison and White's (1942) series, 43 per cent had calcification of the pericardium. However, as stated before, they believed that rheumatic fever is rarely, if ever, an etiologic factor. Monckeberg (1924) was of the opinion that old masses of fibrin which do *not become organized*, gradually become calcified. Very rarely the entire pericardium may consist of many masses of calcium. This condition may be found at autopsy of subjects who had no cardiac symptoms during life.

Nomenclature. Terms describing adhesions between the pericardium and the adjacent structures are varied. The following may clarify the nomenclature. By *adhesive pericarditis* is meant adhesions between the visceral and parietal layers of the pericardium. *Synechia cordis* is the older nomenclature and also *concretio cordis* may be used. Such adhesions may not have produced clinical evidence of disease

If adhesions are found between the outer portions of the pericardium and adjacent structures, the term *mediastinopericarditis* is applied The older nomenclature was *accretio cordis* Mediastinopericarditis may not necessarily cause "inflow disturbances" to the heart It is often seen in instances of old rheumatic fever, accompanied by evidence of old endocarditis The hypertrophy of the heart is often the result of co-existent valvular disturbances. *Constrictive pericarditis* is a form of mediastinopericarditis in which mediastinal adhesions to the pericardium have produced inflow disturbances. Such disturbances may be caused by constriction in the region of the inferior vena cava just as the latter enters the right atrium and rarely by constriction elsewhere in the right atrium or in the ventricle. Rarely, rigid (calcified) layers of the pericardium cause limitation of the diastolic expansion of the heart. Such a pericarditis is also classified as constrictive pericarditis. Angulation of the inferior vena cava in the region close to the openings of the hepatic veins into the inferior vena cava may be caused by mediastinal adhesions (Such patients may have severe ascites, but no edema of the lower extremities) Constrictive pericarditis rarely is caused by rheumatic fever and more commonly, by tuberculosis.

In *Pick's disease* there is constrictive pericarditis with angulation of the inferior vena cava close to the opening of the hepatic veins, and associated polyserositis with perihepatitis and perisplenitis.

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Nonrheumatic Inflammatory Diseases of the Heart
B. Endocarditis

This chapter concerns the various endocardial infections, with the exception of rheumatic endocarditis which will be treated separately (Chapter VIII). This discussion presents the gross morphologic appearance of these endocarditides, how they may be recognized, and their pertinent microscopic features. An attempt is made to point out their incidence, causes, differential morphologic characteristics, the lesions associated with bacterial endocarditis, and their complications. The present day concept of fetal endocarditis and the results of attempts at experimental production of acute and subacute bacterial endocarditis are given. Lesions of the mural endocardium, their genesis, appearance, and functional significance are also considered

In this discussion the pertinent literature is quoted in an effort to keep the various concepts up to date. An effort is made to avoid dogmatism and contentious argument; and quotations that are not supported by proof may be challenged in some instances. Even in this relatively small sphere of pathology there are still a number of unsolved problems. Just what is subacute bacterial endocarditis? Is there an endocarditis caused by toxins? Does endocarditis exist in the absence of verrucae or vegetations? Such unsolved questions are presented with the intention of arousing interest in a particular problem and of stimulating research.

Pathology has cleared the way for clinical medicine in providing an explanation for many clinical signs and symptoms. In this chapter, wherever deemed important, reference is made to clinical medicine and to therapeutic agents It will be obvious that, in order to have a proper understanding of disease in the patient, one must have a knowledge of the pertinent pathologic changes.

Classification of Endocarditis. Terminology. The term *endocarditis* is usually used to designate inflammation of the valvular endocardium, while *mural* or *parietal endocarditis* denotes inflammation of other portions of the endocardium. The only way in which to recognize acute endocarditis grossly is by the detection of verrucae or vegetations attached to the heart valves and the finding of ulcers. Whether or not "valvulitis" can be recognized grossly in the absence of verrucae will be discussed subsequently.

Endocarditis is generally classified as acute, subacute, chronic, and recurrent; also as bacterial, nonbacterial, and syphilitic. Anatomically it is designated as verrucous, vegetative and ulcerative. By *verrucae* are meant minute or small wart-like excrescences. Verrucae will be more fully discussed in the chapter on rheumatic endocarditis (Chapter VIII). It may be merely mentioned here that the earliest changes are probably a swelling of the collagen just beneath the endothelium

covering the valve with slight cellular infiltration. The lining endothelium becomes gradually separated, undergoes necrosis and a small thrombus, consisting principally *of platelets and fibrin, is formed in* this region. Verrucae vary in diameter from about 1 to 4 mm By *vegetations* are meant large thrombi Sometimes the terms "simplex," "productive" or "rheumatic" are used in the same nonspecific sense as "verrucous," and the terms "malignant," "ulcerating" or "necrotizing," to denote vegetative and often ulcerating endocarditis (Kaufmann, 1922) In order to emphasize that both verrucae and vegetations are thrombi, Ziegler (1888) used the term *thrombo-endocarditis superficialis* (or *simplex*) for verrucous endocarditis, and *thrombo-endocarditis septica* (or *ulcerosa*) for vegetative or ulcerating endocarditis. Aschoff (1919) also used Ziegler's nomenclature Clawson (1924), in an analysis of 220 instances of endocarditis, classified active endocardial lesions into bacterial and rheumatic types The former is again divided into acute (primary and secondary) and subacute. The term "primary acute bacterial endocarditis" indicated that no other primary focus of infection existed and "secondary acute bacterial endocarditis," that the endocarditis was associated with another disease, acute or chronic. Gross and Friedberg (1936) recommended use of the following classification of endocarditis:

I Bacterial (bacteria cultivated consistently from blood during life or from vegetations at autopsy)
   A. Acute
   B *Subacute*
      1 With bacteremia
      2 In bacteria-free stage

II. Nonbacterial
   A. Rheumatic
   B. Atypical verrucous
   C. Nonbacterial thrombotic

III. Syphilitic (involving only aortic valve)

The following discussion of acute endocarditis will be based on both the etiologic and anatomic classifications Most forms of acute verrucous endocarditis are the result of acute rheumatic fever, and their gross and microscopic appearances have been discussed in the chapter on Rheumatic Diseases. Nonrheumatic forms of acute verrucous endocarditis include (1) bacterial endocarditis, (2) so-called endocarditis minima (*marantic* endocarditis), (3) the *indeterminate* form of endocarditis and perhaps (4) certain "toxic" forms of endocarditis *Bacterial endocarditis* (the term "infective endocarditis" is more generally used in the British literature), which constitutes the largest of these groups, is caused by well-known micro-organisms, is characterized by the formation of large vegetations, and often shows small or large ulcers and even perforation of the valve. Both acute and subacute bacterial endocarditis fall under this heading These will be discussed separately with respect to their gross and histologic appearances and their etiology Sometimes, however, it is not possible to separate these two types, even after careful study Some overlapping in this discussion, therefore, is inevitable. Both forms, however, will be treated together with respect to complications and associated diseases.

BACTERIAL ENDOCARDITIS

Acute Bacterial Endocarditis

Incidence. It is difficult to obtain from the literature data on the incidence of acute bacterial endocarditis. Thus, Ribbert (1924) in his extensive monograph does not state how frequently such lesions are encountered at autopsy in a general hospital. Buday (1929) found 364 instances of various recent and old fatal valvular diseases in a series of 6155 autopsies. Among these were 87 examples of subacute bacterial and 44 of acute bacterial endocarditis. Martin and Adams (1938) reported 157 instances of vegetative endocarditis in a series of 17,000 autopsies Goldburgh and associates (1942) reported 646 cases of acute bacterial endocarditis in 26,007 autopsies. They found the following valves involved·

Mitral only	308
Aortic only	164
Mitral and aortic	121
Tricuspid only	20
Mitral and tricuspid	10
Aortic, mitral and tricuspid	7
Pulmonic only	5
Aortic and tricuspid	5
Mitral, pulmonic and tricuspid	3
Mitral, aortic, tricuspid and pulmonic	3

Reinhardt (1920) studied 158 cases. He found the valves of the right ventricle only to be involved 15 times, the pulmonic valve nine times, the tricuspid valve five times, and both valves once. In 12 instances, valves of both ventricles were diseased. The aortic valve only was the seat of the disease 50 times, the mitral valve only, 42 times; and both valves, 36 times. Ribbert believed that the aortic valve is the one most often affected. Clawson (1941) found 514 cases of bacterial endocarditis among 30,265 autopsies. In 49 cases with primary acute bacterial endocarditis, death occurred within less than six weeks after the beginning of symptoms. Secondary bacterial endocarditis was found in 101 cases (Table IX-1). Among 1000 consecutive autopsies at Michael Reese Hospital, acute bacterial endocarditis was found 17 times. The mitral valve only was involved 12 times; the aortic valve only, once; and both valves, four times.

TABLE IX-1

Age and Sex Incidence in 151 Cases of Primary Acute and Secondary Acute Bacterial Endocarditis (From Clawson, 1941)

Decade	*Number of Autopsies*	*No of Cases of Primary Acute Endocarditis*	*No. of Cases of Secondary Acute Endocarditis*
	Males		
1	2,978	1	1
2	645	3	1
3	1,324	3	6
4	2,052	3	11
5	3,132	8	8
6	3,439	2	10
7	3,350	4	8
8	2,172	1	3
9	565	0	2
10	28	0	0
Totals	19,685	25	50
	Females		
1	2,208	2	2
2	574	4	2
3	1,174	5	16
4	1,283	8	14
5	1,347	0	5
6	1,411	1	7
7	1,342	2	4
8	930	2	0
9	279	0	1
10	32	0	0
Totals	10,580	24	51

Age and Sex Distribution. Table IX-2, taken from Thayer (1931), shows the incidence of acute bacterial endocarditis caused by several organisms, according to distribution by age in decades.

TABLE IX-2

Incidence of Acute Endocarditis, Caused by Several Bacteria, According to Age by Decades (Thayer, 1931)

Decade	*Streptococcus*		*Pneumococcus*		*Staph aureus*	
	No Patients	%	No Patients	%	No Patients	%
1st	12	6.1	1	3.1	4	12.5
2nd	22	11.2	4	12.5	7	21.8
3rd	55	28.1	22	68.8	6	18.8
4th	47	24.0	3	9.4	6	18.8
5th	26	13.3	1	3.1	2	6.2
6th	24	12.2	1	3.1	6	18.8
7th	10	5.1			1	3.1
All	196	100	32	100	32	100

In streptococcal endocarditis, the percentile distribution between the sexes was equal to that of the ordinary hospital representation: men, 111 (56 6 per cent), women, 85 (43 4 per cent), the same was true as to race. white persons, 152 (77.5 per cent); Negroes 44 (22 4 per cent). Among those with pneumococcal endocarditis, there were more men (71 8 per cent) than women (28 1 per cent), and more Negroes (56 2 per cent) than white persons (43.8 per cent) Subjects with endocarditis caused by *Staphylococcus aureus* were equally represented by the two sexes. Twenty-two (68.7 per cent) were white and ten (31 3 per cent) were Negro Table IX-1 from Clawson gives the age and sex incidence of 49 cases of primary acute endocarditis and 101 cases of secondary acute bacterial endocarditis

In a review of 700 postmortem examinations of persons 60 years old and over, Zeman and Siegal (1945) encountered nine subjects with acute bacterial endocarditis.

Gross Appearance. Acute bacterial endocarditis, vegetative and ulcerating or infective endocarditis, is characterized by large vegetations which vary in size and shape They are situated not only along the line of closure of the valve, but may be present anywhere on the valve and often involve the free margins Large vegetations are often formed by the confluence of smaller ones They vary from 4 mm. to 2 cm. in diameter. Their color is yellowish red or yellowish gray. They usually are attached to the valve by a broad base, but the more superficial portions of the vegetations are soft and break off easily. In such instances, or when necrosis has occurred within the superficial portions of the vegetation, the remaining defect is irregular in contour. At autopsy, often a recent thrombus or clot is found closely attached to this defect. It is thus sometimes difficult to decide which part of the vegetation is older, or the true vegetation, and which part is the superimposed clot. The latter has a characteristic currant-jelly color; it often breaks loose if exposed to a stream of water, or it can easily be separated from the vegetation by means of forceps. The superficial portions of the valves involved by vegetations often become necrotic and when the necrotic material has sloughed away, smaller or larger ulcers are exposed at the free margins of the cusps or leaflets. The adjacent endocardium is red and swollen. It is sometimes difficult to distinguish between an ulcer within the cusp and a defect of an eroding sessile vegetation. The necrotic portion of the valve and the attached vegetation form one unit and may slough off as such. The adjacent border of the cusp is ragged, irregular in outline, and often the seat of minute ulcers situated at the free margin (Figure IX-8).

Frank ulcers of various shapes and forms are common. They may be situated at the free margin of the valve causing a ragged appearance, in the midportion of the valve, surrounded by vegetations, or they may be covered by vegetations Cecil and associates (1948) reported a perforating ulcer of the aortic valve. The perforation apparently became secondarily covered by recent vegetations which, it was believed, had caused an improvement in the patient's condition.

In those instances in which the vegeta-



Figure IX-8 Acute bacterial endocarditis with perforation of anterior leaflet of mitral valve Pneumococcus, Type 25, was recovered from sputum and blood during life, and from lung and valvular vegetation at autopsy From a patient with unresolved pneumonia (WCGH, 40 A 198)

tions are imposed on a valve which previously was normal, the valvular tissue adjacent to the vegetations is usually edematous and reddish but sometimes grossly normal. Allen (1939a) stated that it is generally agreed that acute bacterial endocarditis occurs on a previously existing valvular deformity in from 50 to 75 per cent of cases, but this figure seems, from our experience, too high. In Buday's (1929) series of 31 cases of acute bacterial endocarditis, vegetations were found on normal valves 22 times. Whenever evidence of an older valvular lesion is encountered, the possibility of subacute, as opposed to acute, bacterial endocarditis should be considered.

Location. Most commonly the vegetations of the aortic cusps are located on the ventricular aspect and the vegetations of the mitral leaflets on the atrial aspect. However, when the mitral valve is involved by extension of the inflammatory process from the aortic valve, the endocarditis is, of course, located on the ventricular surface of the aortic leaflet of the mitral valve. The vegetations are often not confined to the valves. The vegetations of the aortic valve may extend to the adjacent aortic intima and produce an acute vegetative endaortitis. There may be a mass of vegetations involving the cusp, the intima facing the sinus of Valsalva and the intima of the adjacent ascending aorta. The vegetations may extend to the mural endocardium of the adjacent interventricular septum or, more commonly, to the aortic leaflet of the mitral valve. The endocarditis of the mitral valve may extend to the endocardium of the left atrium or may involve the chordae tendineae and also the papillary muscles. Occasionally the involved chordae may rupture

Contact and Parietal Endocarditis. Parietal and mural endocarditis may be the result of either direct extension of the valvular endocarditis to the adjacent mural endocardium, or contact of bacteria-laden vegetations with the opposing region of the mural endocardium as the result of the cardiac movements. Such "contact" endocarditis is often encountered on the ventricular aspect of the aortic leaflet of the mitral valve since, in the presence of large vegetations on the aortic valve, this mitral leaflet during diastole is often in contact with the vegetations The occurrence of isolated mural bacterial endocarditis is rare. Ribbert (1924) admitted that he had never seen such an instance but referred to rare reports in the older literature. Thus, Schulz (1884) had reported in a patient with puerperal sepsis, a cloudy, more or less circumscribed area of mural endocardium of the left ventricle which was covered with fibrin and soft thrombi, while the valvular endocardium was not involved. (See also page 721.) There are many instances, however, of small whitish thickenings of the endocardium which sometimes are interpreted as healed mural endocarditis. These will be discussed later.

Valvular Aneurysms. Though, strictly speaking, valvular and erosive endocardial and myocardial aneurysms are classified as complications of acute bacterial endocarditis, for convenience they are discussed at this point. Because of the inflammation and subsequent necrosis of portions of the cusp, and the aortic diastolic pressure exerted upon the sinus of Valsalva, the respective aortic cusp may rupture. The intracardiac pressure may lead to rupture of a necrotic portion of a leaflet of the mitral valve. Sometimes the rupture involves only the midportion of a leaflet. This opening may become covered again by vegetations. However, because of the intracardiac pressure, outpouchings of the friable thrombus in the ruptured portion of the valve occur and false aneurysms ensue. Such false aneurysms occur most frequently on the aortic cusps and less frequently on the aortic leaflet of the mitral valve. Erosive aneurysms may be the result of ulcerations of the leaflet with destruction of the fibrosa (see terminology used by Gross and Kugel, 1931) and extension to the auricularis, leaving the endocardial layer and the auricularis elastic lamellae (leaflet of the mitral) relatively intact. Such aneurysms constitute only a temporary stage, for subsequent perforation is bound to occur. Ribbert (1924), in a detailed discussion, pointed out that it is difficult to distinguish grossly between false aneurysms, the result of primary rupture and subsequent attempted closure of the points of rupture by thrombi, and erosive aneurysms. This is so because a thin layer of fibrin may grossly simulate a thinned-out but preserved valvular endocardial layer, and only a microscopic examination of the outpouchings may reveal its exact nature. Ribbert coined the term "thromboaneurysm" to denote the origin of these false aneurysms. Kaufmann (1922) made a distinction between acute and chronic valvular aneurysms. The former are the result of ulcerating endocarditis with necrosis of the involved portion of the valve. In regard to the latter, he merely mentioned that there may be a "chronic outpouching" of the cusps in endocarditis, which may rupture, but he gave no details. Whether or not those chronic aneurysms are true aneurysms is not stated. It must be noted that true aneurysms of the valves do exist and that they occur in the healing stages of subacute bacterial endocarditis. They will be discussed later.

Erosive Aneurysms. The term "erosive aneurysm" seems preferable to such terms as "embolic" or "mycotic aneurysm."

Terminology. Inasmuch as the terms "embolic," "erosive" and "mycotic" aneurysms are sometimes used interchangeably, it seems desirable to establish a correct nomenclature. *Embolic aneurysms* are the result of the lodging in blood vessels of hard particles which, because of their density, penetrate into the vascular walls and lead to local dilatations (Karsner, 1949). Infected embolic aneurysms are referred to as *mycotic aneurysms* even though "mycotic" literally has reference to a fungus. Such "mycotic" or "infected embolic" aneurysms are caused by infected emboli which either become adherent to the intima of a blood vessel or lodge in vasa vasorum of larger blood vessels. Infected emboli may also lodge on the endocardium and may cause a mural endocarditis and subsequently an embolic aneurysm, or they may be brought to the heart by the coronary arteries. However, if there is an extension of an inflammatory process from an acutely diseased valve of the heart to the adjacent endocardium or to the intima of the sinus of Valsalva with resulting ulcerative mural endocarditis or endarteritis, respectively, and destruction of the myocardium (or media) with consequent local dilation, the term *erosive aneurysm* is appropriate (Karsner). Since erosive aneurysms are the result of infected vege-

tations, or of localization of virulent organisms, they are also "mycotic" aneurysms.

Pathogenesis. Erosive aneurysms also involve the aortic intima, the adjacent endocardium and subsequently also the myocardium close to the involved valve. As a result of a mural or parietal endocarditis, necrosis of the involved endocardium and subjacent myocardium may occur In this event the necrotic material will be gradually excavated by the impact of the blood stream and eventually will slough, leaving a defect of the mural endocardium and myocardium surrounded by inflamed myocardium. Such a defect constitutes an acute myocardial, mural or so-called *cardiac ulcer*. Such an ulcer in the interventricular septum on the left ventricular aspect may cause bulging of the septum into the right ventricle and thus lead to the formation of an erosive mycotic aneurysm Similar ulcerations may be present in other locations and lead to bulging into the pericardial sac. Eventually such erosive mycotic aneurysms may rupture. Rupture into the pericardial sac is almost always preceded by acute purulent or organizing pericarditis. As a matter of fact, Ponfick (1873) has noted that the cardiac wall *often behaves like that of an artery and* the pericardium like the arterial adventitia. Just as the adventitia is thickened over an arterial aneurysm, so is the epicardium thickened by chronic defensive inflammation in the region of the aneurysm. This thickening of the pericardium protects the aneurysm. Rupture of the heart may, therefore, be gradual, with slow leakage of blood into the pericardial sac through one or several small openings, and successive clotting of blood in layers on the surface of the heart The presence of old or recent pericardial adhesions frequently prevents a large, immediately fatal extravasation of blood.

Acute purulent pericarditis is the result of either an extension of the inflammatory process, or of migration of organisms to the adjacent epicardium along the lymphatics. Sometimes mycotic aneurysms which involve the endocardium and myocardium may be caused by infected emboli that arise from vegetations and lodge in coronary arterial branches within the myocardium. Only rarely can there be demonstrated, microscopically, a distention of the involved blood vessel with consequent formation of an embolic aneurysm Much more commonly emboli are noted in branches of the coronary arteries with resulting necrosis, minute infarcts or abscess formation. Such an abscess may extend into the mural endocardium which then is covered with thrombi and also undergoes necrosis. The necrotic material in turn will be sloughed, leaving an ulcer which becomes the seat of a mycotic aneurysm. It may then be impossible to determine whether such a mycotic aneurysm was mycotic embolic or mycotic erosive in origin. A mycotic aneurysm of this type may also perforate into the pericardium or, if present within the septum, into the right or left ventricle or into both ventricles.

Perforation of Aneurysms. Of 15 instances of perforated embolic and erosive *aneurysms of the heart reported by* Pirani (1943), 12 aneurysms were erosive in origin, and only three were embolic. Among 734 instances of cardiac rupture reported by Krumbhaar and Crowell (1925), and by Davenport (1928), abscesses of the heart (probably embolic aneurysms) were encountered only five times. A common *site of rupture* is the ventral wall of the left ventricle close to the atrioventricular groove. Pirani believed that this predilection is to be explained by the particular structure of the myocardial-aortic juncture and by the presence of abundant subepicardial fat, giving this region less resistance. From this area, the septic process may easily extend to the myocardial tissue near the

aortic ring, follow the loose fibrous connective tissue around the large branches of the left coronary artery and thus reach the pericardium. The presence of a pericardial wedge in this region and the proximity of the aortic ring to the pericardium make it possible for an infection originating in the aortic ring area to pass easily by contiguity into the pericardium (Gross and Kugel, 1931). It is also possible that the direction and pressure of the blood stream in the region of the *conus aorticus* further contribute to the excavation and eventual rupture of an endocardial ulcer in that region, more so than in any other area of the cardiac wall Rare *dissecting aneurysms* of the heart following acute vegetative (bacterial) endocarditis are also reported Four cases of Pirani's series were dissecting aneurysms. (See also section on Subacute Bacterial Endocarditis.)

Microscopic Architecture of Normal Heart Valves. Before discussing the microscopic picture of acute bacterial endocarditis, it might be profitable to give a short general description of the human heart valves with relevant illustrations (Figure IX-9) Both the description and illustrations are taken from Gross and Kugel's study (1931) For further details their communication must be consulted

The several heart valves have certain general features in common and yet sufficient individual differences to distinguish them sharply from one another. All the valves carry as a backbone a dense collagenous layer for which Gross and Kugel propose the term *fibrosa* On the atrial aspect of the atrioventricular valves, as well as on the ventricular aspect of the semilunar valves, the fibrosa shows a loose structure which they call *spongiosa* In the semilunar cusps this looser structure may be so conspicuous as to constitute a sharply defined layer. Each valve cusp is attached at its base to a more or less dense connective tissue structure called *annulus fibrosus* The extent, distribution and connections of the annulus differ considerably with the various cusps. Its topography for the aortic valve has been described by Lewis and Grant (1923). It constitutes an important strategic site which includes part of the base of the valve as well as the adjacent portion of the annulus Gross and Kugel designate this area as the *ring.* The rings of the semilunar valves generally contain a conspicuous spongiosa, while the atrioventricular valvular rings in this area show only a slightly looser structure of the collagenous fibrosa, designated *ring spongiosa* The *fibrosa,* with its looser layer, is clothed on both sides by a continuation of the arterial intima or ventricular or atrial endocardium, as the case may be. These arterial or endocardial connective tissue mantles contain more or less conspicuous elastic sheets. The elastic sheets which are situated on the outflow surface of the valve (atrial surface of the atrioventricular valves and ventricular surface of the semilunar valves) are generally the heavier and longer. Both elastic layers thin out progressively as they approach the tip of the valve

As a generalization, it may be stated that while the separation of these layers of the valves is already seen in early fetal life, they become more and more clearly defined in advancing postnatal life Furthermore, the differences in their extent, thickness, structure and distribution give to each cusp, its individual characteristics Figure IX-9, taken from Gross and Kugel's article, outlines the more important histologic details of the valves

Histologic Changes in Acute Bacterial Endocarditis. An excellent description of the pertinent histologic changes is found in Ribbert's monograph (1924). The vegetations of acute bacterial endocarditis consist principally of masses of *fibrin* with very few platelets and with minute crevices containing varying numbers of red blood cells

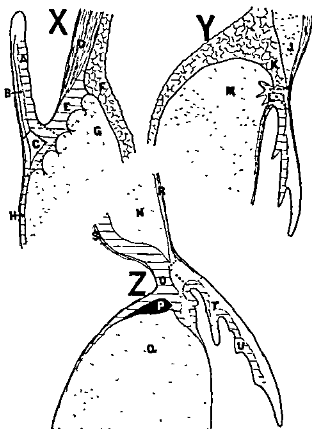


Figure IX-9 Diagrams of typical semilunar and atrioventricular valve rings

X Typical semilunar cusp A, fibrosa, B, valve spongiosa, C, ring spongiosa, D, aorta, E, annulus, F, pericardium, G, ventricular myocardium, H subvalvular annulus Area enclosed by dotted lines is the valve ring

Y Typical arterioventricular leaflet, I, atrial myocardium, J, atrial myocardial wedge, K, pericardial wedge, L, annulus, M, ventricular myocardium Area enclosed by dotted lines is the valve ring

Z Typical septal flap of tricuspid valve section N, right atrial myocardial wedge, O, septum fibrosum, P, bundle of His, Q, interventricular septum, R, right atrial endocardium, S, left atrial endocardium, T, valve spongiosa dipping into the chorda tendinea insertion, U, valve fibrosa Area enclosed by dotted lines is the valve ring

(Reprinted from Gross and Kugel *Am J Path*, 7.445, 1931, by courtesy of *American Journal of Pathology*)

Intermingled in this mass of fibrin are large clumps of *bacteria* (cocci). Often they extend in dense accumulations over the margins of the leaflets. If thrombi are already formed, the cocci may be found within them in the form of polymorphous areas of "cloud-like" accumulations. They may be covered with fibrin or, less commonly, they may form the most superficial portion of the thrombus. They are often located between the substance of the valve and the *thrombus*. The lining *endothelial cells* of the valves early disclose various degenerative changes, eventually become necrotic and finally disappear. Relatively more rarely than is seen in subacute bacterial endocarditis, some of the lining endothelial cells become larger, more cuboidal in shape and contain two or three nuclei. Such giant cells may contain a few cocci within their cytoplasm.

Are the Vegetations Thrombi? Most observers believe that the vegetations of bacterial endocarditis are thrombi. However, Allen (1939b), because of his interpretation of the histologic evidence, and particularly because of the presence of elastic elements within the vegetations, does not consider them to be thrombi deposited from the blood on an inflamed endocardial surface He believes rather that the vegetations are principally derived from necrotic valvular tissue, forced apart by the plasma and blood elements exuded by the eroded or abnormally permeable blood vessels found in inflamed valves. Moore (1946) also maintained that the vegetations consist of portions of necrotic valvular tissue.

Role of Bacteria. The cocci obviously multiply rapidly and extend into the substance of the leaflets. Necrosis of various portions of the valve ensues. The necrosis is found first in the region of the ventricularis, the fibrosa of the valve being spared. Only later are all layers of the valve substance involved in the necrotizing process. The necrosis obviously is the result of the bacterial toxins. It may be diffuse; or it may involve certain portions of the leaflet more severely and thus extend in these localized areas through the entire thickness of the leaflet and cause early perforation.

Inflammatory Changes. At first the valvular tissue reacts slowly toward the



Figure IX-10 Vegetation of acute bacterial endocarditis. Note area of necrosis and accumulation of polymorphonuclear leukocytes. Iron-hematoxylin X 125.

infection The principal early changes are necrosis and the presence of cocci Next, the tissue becomes edematous and fibrin appears, the latter perhaps being an extension into the valve of the fibrin which constitutes the vegetation Few endothelial leukocytes multiply within the valve Where blood vessels are present (in old inflamed valves), hyperemia is marked and exudation of polymorphonuclear leukocytes ensues. Most of the latter, however, are found external to the elastic lamellae, indicating perhaps their origin from the passing circulating blood However, if it is true that blood vessels exist normally at the base of the valve and at the lateral borders of the aortic cusps, as some investigators (Bayne-Jones, 1917; Wearn, Bromer and Zschiesche, 1936) maintain, it can be well understood that these vessels may be the source of the exudation. Gradually polymorphonuclear leukocytes, fibrin and bacteria form large masses within and adjacent to the valve substance. Still later, more polymorphonuclear leukocytes accumulate (Figure IX-10) at the border between the necrotic valve and the adjacent tissue In more severe cases, however, the whole cusp or leaflet is involved in the necrotizing process and masses of polymorphonuclear leukocytes also become necrotic. Without staining for elastic fibers, it is often impossible to judge which part of the necrotic mass represents the remains of the valvular tissue and which the necrotic thrombus. The presence of elastic lamellae indicates the remains of valvular tissue. It is easily understood how such masses of necrosis, giving way to intracardiac pressure, are swept away, with ensuing tearing and ulceration of the valve

Organization. In those instances in which the necrosis is not diffuse, early evidence of organization can be noted. Buds of endothelial cells, sprouting from blood vessels at the base, extend into the masses of necrosis with formation of capillary vessels, and young connective tissue cells appear at the margins of the necrosis. As Ribbert stated, the very young blood vessels and rows of fibroblasts extend beneath, and parallel to, the thrombi. Leukocytes migrate from these newly formed vessels, a serous exudate infiltrates the adjacent valvular substance and fibrin is deposited. Thus, characteristic layers of fibrin appear within the leaflet with polymorphonuclear leukocytes and monocytes within the meshes of the fibrin (Ribbert, 1924). This material penetrates or surrounds areas of necrosis, extends into the thrombi and eventually forms one mass of granulation tissue.

Sequelae. At the free margin of the vegetation in both acute and subacute bacterial endocarditis, precipitation of *calcium salts* is early disclosed Ribbert believes that the deposition of calcium is especially marked in the region of the aortic valves, at the most lateral portions of the cusps where they are attached at the aorta (commissures). This will be more fully discussed later. It seems clear that because of the bacteremia, because of the severity of the valvular lesions and because of the associated myocardial damage and embolic phenomena, acute bacterial *endocarditis* is a disease that often causes death in a

short time However, it is conceivable that in the absence of any complications, even without specific therapy, the organization of the exudate and the granulation tissue of the valve may result in cicatrization with resulting *deformities* and complete *healing* It stands to reason that with modern therapeutic measures combatting the bacteremia on one hand and preventing further formation of thrombi on the other, more patients with acute bacterial endocarditis will survive. Thus, it should be remembered that old valvular deformities also may be the result of acute bacterial endocarditis and must not necessarily always be considered to have been caused by acute rheumatic endocarditis.

Endocarditis without Vegetations. Ribbert (1924) discussed the question, whether acute valvular endocarditis can be diagnosed in the absence of thrombi or vegetations He believed that this is theoretically possible since, adjacent to vegetations, a rough or finely granular valvular endocardium is sometimes seen. Yet, if in very rare cases only such a finely granular endocardium is encountered, microscopic examination invariably discloses flat thrombi consisting principally of fibrin He, therefore, concluded that an endocarditis without verrucae or vegetations does not exist. This statement must be seriously questioned. One sees, not rarely, in association with acute rheumatic endocarditis of the mitral valve slightly red-tinged, swollen cusps of the aortic valve which seem to have lost their turgor and appear wrinkled There are no verrucae present and their surfaces are glistening. Histologically, such cusps are the seat of an edema or of a fibrinoid degeneration of the collagen. This condition probably represents very early inflammation of the valve. (See Chapter VIII on Rheumatic Endocarditis.) In the absence of verrucae this inflammation should be termed "acute valvulitis." It is likely that similar changes may be present in very early instances of bacterial endocarditis. Unfortunately, such studies are not available. It might be of interest, therefore, to study microscopically the aortic and mitral valves in instances of acute infectious diseases which grossly show no changes, to determine if early changes within the valves in the absence of vegetations may be detected.

Causes of Bacterial Endocarditis. Bacterial endocarditis may result from almost any bacteremia or septicemia. It may be incidental to septicemia and of no particular influence upon the course of the disease. It may prolong the septicemia by serving as a secondary focus for the spread of organisms; or it may constitute the principal feature of the disease, and because of embolic complication, cause death. Karsner (1949) enumerates the following diseases which may be complicated by endocarditis: pneumonia, osteomyelitis, septicemias and pyemias resulting from wounds and infections incident to childbirth and other causes, typhoid fever, scarlatina, diphtheria, measles, variola, influenza, tuberculosis, gonorrhea, and other infectious diseases. The endocarditis which accompanies infectious diseases is caused by the organisms of those diseases in some instances, and by what appears to be secondary invaders in others.

Causative Organisms. Probably most virulent micro-organisms may be found associated with endocarditis. Karsner (1949) mentions the following bacteria as being especially associated with acute endocarditis *Haemophilus influenzae,* the viridans group of streptococci, *Neisseria gonorrhoeae, Staphylococcus aureus, Staphylococcus albus, Diplococcus pneumoniae,* the hemolytic streptococci and meningococcus. Also *Brucella abortus* and higher organisms such as Actinomyces and other fungi have been reported to have caused endocarditis. Whereas *Streptococcus viridans* is encountered in a vast

majority of instances of subacute bacterial endocarditis, this organism has also been reported in acute bacterial endocarditis. The following table (Table IX-3) is taken from Thayer (1931) It is included here to show the relative frequency of valvular involvement by various bacteria. However, as stated above, both acute and subacute bacterial endocarditis are included in his discussions.

TABLE IX-3

Causative Bacterium in 306 Instances of Infective Endocarditis, According to Thayer (1931)

Organism	*No. of Cases*	*Per Cent*
Streptococcus	191	62 4
Pneumococcus	38	12 4
Gonococcus	31	10 1
Staphylococcus aureus	28	9 2
B influenzae (Pfeiffer)	9	2 9
Staphylococcus albus	6	2 0
B. pyocyaneus	1	0 3
B. anthracis	1	0 3
B friedlanderi	1	0 3

From this table it is obvious that the Streptococcus is the most common cause of bacterial endocarditis Table IX-4 indicates the frequency of involvement of the two sides of the heart in bacterial endocarditis produced by these organisms

TABLE IX-4

Causative Organisms in Relation to Frequency of Side of Heart Involved, According to Thayer (1931)

Organism	*Left Side*	*Right Side*	*Both Sides*	*Total Cases*
Streptococcus	78	5	16	99
Pneumococcus	30	3	4	37
Staphylococcus aureus	18	6	3	27
Staphylococcus albus	4	2	0	6
Gonococcus	17	6	4	27
B. influenzae (Pfeiffer)	4	1	2	7
B pyocyaneus	1			1
B anthracis	1			1
B friedlanderi		1		1
Totals	153	24	29	206

Table IX-5 from Moore (1944) is included to show the valves involved by the more commonly encountered bacteria Both Tables IX-4 and 5 indicate that the valves of the left ventricle are much more

TABLE IX-5

Frequency of Involvement of Various Valves by Several Common Bacteria, According to Moore (1944)

Valve Involved	*Streptococcus hemolyticus*	*Streptococcus viridans*	Pneumococcus	Staphylococcus	Gonococcus
Aortic	59	53	76	50	70
Mitral	76	82	50	43	37
Pulmonic	6	3	24	25	10
Tricuspid	20	8	4	4	12

commonly involved than those of the right According to Moore, the aortic valve is the seat of acute bacterial endocarditis more often than is the mitral valve, hemolytic streptococci cause endocarditis of the tricuspid valve relatively often, and the pulmonic valve is affected more often by Staphylococcus and Pneumococcus than by other organisms

SPECIAL FORMS OF ACUTE BACTERIAL ENDOCARDITIS

The various endocarditides will be discussed from the point of view of the causative organisms.

Acute Streptococcal Endocarditis. Streptococci are the organisms most commonly associated with bacterial endocarditis. It is usually emphasized that the less virulent forms of streptococci give rise to subacute bacterial endocarditis. In over 90 per cent of cases in Libman and Friedberg's series (1948) the causative organisms were nonhemolytic streptococci, usually of the alpha (viridans) and only occasionally of the gamma (anhemolyticus) variety. (See also page 737) Thayer (1931) stated that 60 per cent of all bacterial endocarditides are caused by streptococci It is stressed repeatedly that infections due to beta-hemolytic streptococci run a rapid course characteristic of septicemia. Endocardial lesions, either small or large, are present at the line of closure or free border of the valves and affect principally the mitral and aortic valves.

Librach (1947) reported an instance of

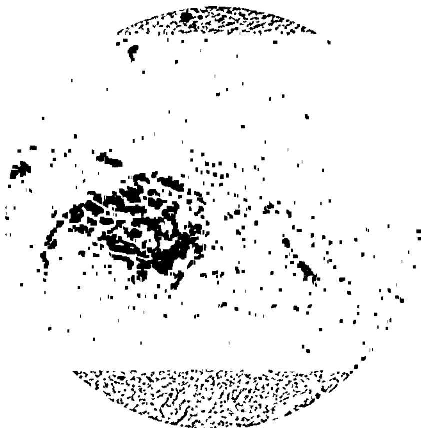


Figure IX-11 Acute bacterial endocarditis caused by *Staphylococcus albus* Embolism to a small coronary artery Note necrosis and perforation of wall of vessel and periarterial inflammation X 135 (WCGH, 40 A 146)

infective endocarditis caused by *Str. viridans,* involving the aortic and tricuspid valves. No mention was made of older valvular lesions. Though this instance was classed as subacute bacterial endocarditis, from the description it seems more likely that it was an acute bacterial endocarditis.

Staphylococcal Endocarditis is not rare. Endocarditis is produced by *Staphylococcus aureus* more often than by *Staph. albus.* Thayer emphasized that the course is rapidly fatal, that often the endocarditis is overshadowed by the clinical picture of the generalized infection and that the endocarditis, therefore, is rarely recognized clinically, being discovered only at autopsy. The valves of the left side of the heart are involved much more frequently than those of the right side. The vegetations are soft and usually not large. The source of the infection, such as osteomyelitis, puerperal sepsis or a carbuncle, is usually easily recognized. Often in such infections metastatic pyemic abscesses are also noted, and they may also be present in the myocardium. In endocarditis caused by *Staphylococcus albus* (Figure IX-11) endocardial lesions are more destructive, and the vegetations are polypoid and large.

Pneumococcal Endocarditis. The older literature, but also relatively recent reports (Goldburgh *et al.,* 1942; Allen, 1939a), stated that pneumococcal endocarditis involved principally the valves of the right side of the heart.

From Thayer's and Moore's tables this is obviously not so. Of 37 cases of such an endocarditis, 30 involved only the left side of the heart. Of 150 instances reported in the literature and collected by Tinsley (1945), 117 involved the left ventricle, 17 the right and 16, both ventricles. In 90 of

the 117, more details were available, the distribution of the endocarditis in these cases being listed in Table IX-6 (See Tinsley; see also Ruegsegger's publication, 1938, for pertinent literature.)

TABLE IX-6

Frequency of Involvement of Various Valves by Pneumococcus, According to Tinsley (1945)

Valve Involved	*Number of Cases*	*Per Cent*
Aortic	32	36
Mitral	30	33
Tricuspid	11	12
Aortic and mitral	7	8
Aortic and tricuspid	6	7
Mitral, aortic and tricuspid	1	1
Mitral, tricuspid and pulmonic	1	1
Mitral, aortic, tricuspid and pulmonic	2	2

Tinsley also remarked that the Pneumococcus produces endocarditis in 3 to 3.5 per cent of all pneumococcal infections and is responsible for from 5 to 10 per cent of deaths caused by pneumococcal infections Karsner (1949) remarked that about 4 per cent of cases of pneumonia develop endocarditis, but in only about one-half of these instances is the Pneumococcus found, other bacteria recovered probably being secondary invaders (Locke, 1924). The vegetations of pneumococcal endocarditis vary in size but often are huge and not rarely fill the entire valvular areas. They may be present on the mural endocardium *leaving the valvular endocardium intact.* Erosion of the valves with ulcerations (Figure IX-8) and mycotic (false) aneurysms occur commonly. According to Tinsley, pre-existing valvular disease is believed to have little effect on the occurrence of pneumococcal endocarditis Ruegsegger emphasized the occurrence of endocarditis caused by Pneumococcus in the higher age groups and Zeman and Siegal (1945) found four instances of pneumococcal endocarditis among nine patients with acute bacterial endocarditis who were between 60 and 87 years old.

Gonococcal Endocarditis. Thayer (1922) stressed that the anatomic lesions in gonococcal endocarditis were those of a vegetative and ulcerative endocarditis, sometimes spreading to the walls of the ventricles or into the sinuses of Valsalva, and often being associated with extensive destruction of valves and with aneurysmal formation. Sometimes also the adjacent myocardium was infiltrated, with resulting purulent myocarditis. The vegetations were large, brittle and yellowish gray

The aortic valve in Thayer's series (20 cases) was affected six times, the mitral valve twice, and both the aortic and mitral valves also twice *The mural endocardium* of the left ventricle was involved twice The pulmonic valve was the seat of endocarditis four times, and the tricuspid once. Both aortic and tricuspid valves were involved twice, and aortic, pulmonic and tricuspid valves once. Pre-existing valvular disease was present in 20 per cent of Thayer's original series. Among Williams' 10 instances (1938), the mitral valve was affected five times, the aortic valve four times, and both valves once The valves of the right ventricle were not involved. In a series of 93 instances, combining Thayer's (1931) and Kirkland's (1932) reports, aortic lesions were present 41 times; mitral lesions, 20, pulmonic, seven, and tricuspid lesions only once. In 24 hearts more than *one valve was involved It is obvious that* the left side of the heart is involved much more often than the right side. Yet, Thayer (1931) thought it was significant that among five instances without autopsy, two showed clinically an apparent involvement of the pulmonary valve, from which impression he concluded that pulmonic involvement seems to be rather characteristic of gonococcal endocarditis. He also quoted a personal communication from Warthin (1931), who found that among nine patients with gonococcal endocarditis, the pulmonic valve was involved eight times. This finding is not in agreement with the observation of other investigators. Thayer

(1931) stated that the Gonococcus generally attacks previously unaffected valves. Among Williams' 10 hearts, only one disclosed evidence of a pre-existing endocarditis. Karsner (1931), and Hoffman and Taggart (1932) believed that only those instances should be classified as gonococcal which show the presence of gonococci in the blood or vegetations. In spite of this rigid criterion, Williams concluded that gonococcal endocarditis is not rare. Twenty-seven per cent of bacterial endocarditis in his series was attributed to the Gonococcus In fact, Davis (1940) remarked that gonococcal endocarditis is a fairly common disease.

Meningococcal Endocarditis is apparently rare Whillans (1940) stated that only 20 cases of meningococcal endocarditis had been reported up to the time of his report. To verify the diagnosis, the organism should be cultured from the blood, the vegetation, the cerebrospinal fluid or the meninges The presence of intracellular gram-negative diplococci alone is not sufficient as proof However, the demonstration of these intracellular gram-negative diplococci in the vegetation of a patient who also shows either the gross characteristic exudate in the meninges or intracellular diplococci within the cerebrospinal fluid seems sufficient for proof, since gonococci practically never localize in the meninges or cause meningitis

Meningococcal endocarditis can occur as a complication both of meningitis and of meningococcal septicemia Its occurrence as a primary disease entity (Firestone, 1946) is questionable. Herrick (1919) found one instance of endocarditis caused by Meningococcus among 208 patients with epidemic cerebrospinal meningitis. MacMahon and Burkhardt (1929) stated that about half of the cases of meningococcal endocarditis have followed meningitis.

Firestone stated that in reports of 19 pertinent autopsies, which he cited, only three gave evidence that old chronic valvular disease was present in addition to the acute valvulitis. He also stated in reports of 26 autopsies, in which data were given as to the location of the vegetations, the mitral valve alone was involved in 17, the aortic in three, both these valves in five, and both the aortic and tricuspid valves in one. The vegetations were large, massive and yellowish pink, and often covered an entire leaflet. Direct smears usually showed many gram-negative cocci. Ulcerations are less common than in other types of endocarditis, particularly gonococcal endocarditis. Miller's report (1944) is noteworthy. He found meningococcal endocarditis in immunized horses. He suggested that there is an initial endothelial (endocardial) edema which gives rise to a separation of the endothelial layer from the subendothelial tissue; and that these early changes may be the result of an "alteration in the course of the immunization" which produces an endothelium "more vulnerable to the toxic products" of the Meningococcus. The bacteria later localize on the surface of the damaged endothelium. Whillans emphasized the lack of associated meningitis in his case and in approximately one-half of the cases reported. He also remarked that this fact and the increasing number of cases of meningococcal septicemia reported which fail to show evidence of a primary infection in the meninges indicate a "versatility" of the organism beyond that signified by its name.

Salmonella Endocarditis. Wells (1937) reviewed the literature of endocarditis caused by organisms of the *typhoid* group. In 320 autopsies of patients with paratyphoid infection, endocarditis was observed only once. He stressed that typhoid fever and paratyphoid infections rarely cause inflammation of the heart valves. It seems probable that the greater pyogenic tendency of paratyphoid infections may

account for endocarditis occurring somewhat more frequently in these infections than in typhoid However, too few necropsies of cases of paratyphoid fever are reported to permit conclusive determination

Meyer and Howell (1938) reported an instance of acute vegetative endocarditis of the aortic and mitral valve caused by *Salmonella paratyphi B* There was also an early mycotic aneurysm of the sinus of Valsalva The endocarditis was superimposed upon old lesions of the aortic and mitral valves. A new Salmonella *(S fayed)* as the cause of endocarditis was described by Anderson and associates (1947). Cardiac complications in salmonella infections, as have been described in the literature, have also been reviewed by Shulman (1947). Fatal bacterial endocarditis due to *S cholerae-suis* was reported by Forster (1939), Read (1939), and Goulder and associates (1942) None of the patients gave a history of gastroenteritis and the portal of entry was not apparent Most of them showed evidence of pre-existing damage to the affected cardiac valves. Of the two instances reported by Forster, one showed syphilitic changes in the aorta and the other presented evidence of previous rheumatic disease. In the case reported by Read, the heart had no apparent pre-existing valvular abnormality, but in that reported by Goulder and associates the heart showed old rheumatic changes. Massive friable vegetations on the aortic valve with severe ulceration caused by *Salmonella minnesota* were found by Kurz and associates (1949).

Brucella Endocarditis. Scott and Saphir (1928) studied a heart which disclosed acute vegetative endocarditis of the mitral valve superimposed upon an old endocarditis. Firmly attached to the base of the aortic leaflet of the mitral valve on its atrial surface was a soft, round, reddish gray vegetation, measuring 2 5 cm. in diameter. The vegetation partially occluded the already narrowed orifice of the mitral valve. Blood cultures disclosed the presence of *Brucella abortus.* Scott and Saphir were not certain that the endocarditis was actually produced by the Brucella organisms, but suggested the possibility that this might have been an instance of brucellemia in a patient who also had acute bacterial endocarditis, in spite of the fact that no other organisms were noted. Levy and Singerman (1938) collected five additional cases from the literature and reported a case in which the endocarditis had involved the mitral valve The vegetation was large, measuring over 1 cm. in diameter This recent endocarditis was superimposed upon an old endocarditis.

Spink and Nelson (1939) stated that Brucella endocarditis is an infrequent complication of brucellosis. It may be caused by any one of three varieties of Brucella They reported an instance of endocarditis which had involved the aortic valve and caused a large defect of the posterior cusp Wechsler and Gustafson (1942) described endocarditis caused by *Br melitensis* on a congenital bicuspid aortic valve. Whether this was a true bicuspid aortic valve or the result of an old endocarditis (see Koletsky, 1943) cannot be judged from this report. Call and associates (1944) reported two additional instances In one the endocarditis was present on the aortic valve and in the other on the mitral valve. They concluded that among the peculiarities of this type of endocarditis are the tendency to involvement of the aortic valve, the tendency to ulceration and perforation, and the granulomatous nature of associated visceral lesions. Degowin and associates (1945) found the free margins of the mitral leaflets moderately fibrosed. The anterior leaflet of this valve contained a perforation measuring 7 mm in diameter. At the superior margin of the perforation was a friable grayish yellow vegetation 1 cm in diameter. Smaller, but similar, vegetations

were attached at the periphery of the perforation. Several small, firm yellowish pebbled masses were found along the remainder of the line of closure. In Beebe and Menleely's (1949) case the recent endocarditis was superimposed upon an old endocarditis *Brucella suis* was isolated in pure culture during life repeatedly from the blood stream and, after death, from the vegetations of the valve. The patient died from rupture of a mycotic aneurysm of the left femoral artery.

Endocarditis Caused by *Pseudomonas aeruginosa*. Fish and associates (1937) studied an instance of infection with *Pseudomonas aeruginosa* (B. pyocyaneus) associated with bacterial endocarditis. They believed that such an endocarditis is rare (Consult Fish *et al.* for literature.) Many of these instances have been reported in children. They stated that the most interesting feature of this infection is the affinity of the organism for the wall of arteries. They described a yellowish red, shining mass, measuring 0 75 cm. in diameter, attached quite firmly to the aortic valve It was present on both the aortic and ventricular aspects of the involved cusp. There was also an acute aortitis. No old lesions were encountered in the valves Moragues and Anderson (1943) reviewed the literature and reported an additional instance of endocarditis due to *Pseudomonas aeruginosa* They emphasized the importance of the genitourinary and gastrointestinal tracts as portals of entry. The endocarditis had involved the mitral valve which was the seat of a previous endocarditis. The atrial surface of the mitral valve contained large, extremely friable, grayish vegetations and several ulcers were noted but there was no perforation of the valve. Some of the vegetations extended to the endocardium of the left atrium.

Endocarditis Produced by Other Organisms. Craven and associates (1940) reviewed 36 cases of endocarditis caused by *Hemophilus influenzae* and *H. parainfluenzae* (Pfeiffer). They reported two cases of endocarditis caused by *H. parainfluenzae* (nonhemolytic). They stated that in most of the instances of endocarditis reported to have been caused by *H. influenzae*, in retrospect, *H. parainfluenzae* could not be ruled out as the causative agent. They remarked that the endocardial vegetations are of the vegetative ulcerative type and are often, but not always, superimposed on old rheumatic valvular lesions. In five of the 36 cases reviewed, there was unmistakable clinical or necropsy evidence of meningitis They concluded that the high incidence of meningitis, often of distinct chronicity, suggests that the infection of the leptomeninges antedates the endocardial lesions. An instance of a bacterial endocarditis interpreted as resulting from *H. hemolyticus* and *Streptococcus viridans* infection was reported by De Santo and White (1933).

Fletcher (1947) reviewed the literature on endocarditis caused by *E. coli.* He emphasized the proliferative nature of the vegetations, the fact that the infection usually occurs as a postoperative complication, and that it may attack a normal valve. A case of massive vegetative endocarditis of the pulmonic valve caused by a *Paracolon bacillus* was reported by Robertson (1947). (Consult Robertson for literature on endocarditis produced by these organisms.) The other cardiac valves were normal. It was thought that the valvular lesion and the septicemia were secondary to infected polycystic kidneys

An apparently unique instance of bacterial endocarditis due to *Clostridium welchii* has been reported by More (1943). There are also instances of bacterial endocarditis reported where two or more organisms were cultured repeatedly from the patient's blood. Such cases have been recently collected by Organ and Poston (1942).

For reports on endocarditis caused by *Micrococcus pharyngis siccus* and related organisms, see Weed and associates (1943).

MYCOTIC ENDOCARDITIS

Cassels and Steiner (1944) reviewed critically the available literature on mycotic endocarditis Primary infection of the endocardium with higher organisms is distinctly uncommon.

In an autopsy which they performed on a 14-year-old white boy, the mitral valve contained an almost continuous row of vegetations which were rough, warty and mottled yellow and red, friable but firmly attached. The aortic valve had a single large vegetation. There were no old valvular lesions. Colonies of micro-organisms were found scattered throughout the vegetations. The organisms took the form of long, slender filamentous branching rods or of small, round or oval bodies, and both forms were gram-negative and not acid-fast. Such micro-organisms were also found in myocardial and epicardial abscesses, in an infarct of the spleen, in small renal foci of suppuration and in the intestines While the organisms could not be specifically identified, the authors pointed out that the appearance of the growth on culture and in microscopic sections was the same. *There was no evidence that the fungus infection could have been superimposed on a previous bacterial infection*

Beamer and associates (1945) reported two cases of vegetative endocarditis, one caused by *Actinomyces graminis* and the other by *Histoplasma capsulatum*. In the former the mitral and aortic valves were moderately thickened and the seat of numerous *firm, grayish white vegetations On* microscopic examination the organisms were pleomorphic The second case disclosed a thickened aortic valve with a friable vegetation involving both its ventricular and aortic surfaces. Histoplasma was recognized in macrophages. A syphilitic aortitis which had extended to the aortic valve was also noted. These authors also reviewed instances of vegetative endocarditis caused by higher bacteria, yeasts and fungi, including Candida (Monilia), Actinomyces, Leptothrix, Erysipelothrix and Histoplasma. Wedding (1947) also reviewed the literature and described two instances of actinomycotic endocarditis. One was characterized by the clinical picture of subacute endocarditis but the other was not recognized clinically.

Endocarditis caused by *Candida albicans* was found superimposed on a healed (subacute bacterial) mitral endocarditis by Geiger and Durlacher (1947). Recent vegetations involved the chordae tendineae of the mitral valve and the left atrial endocardium Blevins and MacNeal (1946) recovered Actinomyces from two patients In one patient with bacterial endocarditis a branching filamentous organism in cultures was obtained on four occasions. This organism exhibited the characteristics of a micro-aerophilic Actinomyces, was irregularly gram-positive and not acid-fast It was termed *Actinomyces septicus* Large vegetations were situated on the mitral valve, which was ulcerated. The myocardium disclosed acute focal inflammation Basophilic clumps and clusters intermingled with polymorphonuclear leukocytes were recognized microscopically. Cultures from the mitral valve showed various coccoid organisms, but inoculation of the organism into a rat resulted in infection of the animal and recovery of Actinomyces in pure culture The second patient presented the clinical picture of subacute endocarditis. Friable, verrucous *structures were found on the aortic cusps,* while on microscopic examination septated filaments were found in necrotic portions of the aortic and mitral valves. An anaerobic strain of Actinomyces was re-

covered from vegetations of the aortic valve

ENDOCARDIAL TUBERCULOSIS

The tubercle bacillus may also cause endocarditis. Baker's article gives an excellent resumé of reported instances up to that time (1935). His own observations are based on the examination of seven pertinent instances He classified endocardial tuberculosis as follows· (1) endocardial tubercles in miliary tuberculosis, (2) polypoid tubercles, (3) tuberculous nodules on the valves, and (4) tuberculous thrombi. The last may result from tubercle bacilli being trapped in a thrombus, the thrombus then being transformed into tuberculous granulation tissue However, it is more likely that most of the "tuberculous thrombi" recorded were tubercles primarily and that thrombi formed secondarily.

Criteria for Diagnosis. The diagnosis of tuberculous endocarditis should be accepted only if (a) microscopic sections are characteristic of a tuberculous lesion, (b) tubercle bacilli are demonstrable in the lesion, and (c) other causes of endocarditis are excluded. Neither the presence of tubercle bacilli in the blood nor the demonstration of widespread tuberculosis elsewhere in the body should be taken as evidence of the tuberculous nature of the endocardial lesion.

Origin. Scattered tubercles of the endocardium may arise by implantation through the coronary arteries or directly from the circulating blood, and by extension from pericardial or myocardial tuberculous masses.

In an interesting report, Dressler (1921) tells of a child with generalized miliary tuberculosis in whose heart he found a polypoid excrescence on the aortic leaflet of the mitral valve. On microscopic examination this proved to be typical tuberculous granulation tissue. He classified this as a primary tuberculous endocarditis. He quoted Weigert as saying that miliary tubercles are almost always present in the myocardium in instances of generalized miliary tuberculosis. This opinion, however, is not generally accepted. Two instances of tuberculous endocarditis were reported by Davie (1936). Vegetations resembling the verrucae of rheumatic endocarditis were found on the mitral and aortic valves in one, and only on the mitral valve in the second instance. Davie assumed the existence of a tuberculous "allergic" endocarditis. His theory postulates the unusual coincidence of a tuberculous bacillemia and the development of a stage of allergy against tuberculosis. Tuberculous endocarditis of the pulmonary valve was studied by Mark (1938) He found a tuberculous polypoid vegetation on a cusp of the pulmonary valve in a patient with generalized miliary tuberculosis. Bevans and Wilkins (1942) found tuberculous endocarditis of the mitral and aortic valves The aortic valve was also congenitally malformed. In addition to the characteristic granulation tissue, large numbers of eosinophils were present. This finding, they believed, supported Davie's hypothesis. Gilmore (1940) found within the sinus of Valsalva of the right anterior cusp of the pulmonary valve a yellowish, firm, irregularly shaped mass firmly adherent to the proximal portion of the cusp. On microscopic examination this mass consisted of typical tubercles with central areas of necrosis surrounded by small round cells, endothelial leukocytes * and giant cells. The process involved the valve ring but did not extend into the myocardium. Acid-fast bacilli were demonstrated in the valvular lesions. The patient

* The term "endothelial leukocyte" (Mallory) denotes the large mononuclear phagocyte, a cell almost as ubiquitous throughout the tissues of the animal body as the connective tissue itself, and one reaching prominence in many inflammatory exudates. It is pre-eminently phagocytic in function Other terms used for endothelial leukocyte are "epithelioid cells," "polyblast," "clasmatocyte," "histiocyte"

had advanced tuberculosis of the prostate, dorsal vertebrae and lungs with terminal miliary dissemination

Symptoms. Dressler emphasized that tuberculous endocarditis *per se* may produce no clinical symptoms. In tuberculous valvulitis, there is no special predilection for the line of closure Only in rare instances in which caseous nodules involve the valves is the cardiac function affected.

Syphilitic disease of the aortic valve will be discussed under a separate heading (see page 759)

TOXINS AS CAUSES OF ENDOCARDITIS

Ribbert (1924) discussed the possibility of bacterial toxins causing endocarditis. While this is denied, he believes that it is possible that toxins may injure the valves and cause *loosening of the valvular endothelial cells*, with degenerative changes and subsequent repair, there is, perhaps, a resulting cellular proliferation but *no outspoken endocarditis*. These changes are sometimes encountered in diphtheria and typhoid fever Ribbert does not believe that a vegetative endocarditis can possibly be superimposed on these changes in the absence of micro-organisms. Though there are experimental data regarding sensitization of valves with various products of bacteria (see Chapter VIII on Rheumatic Fever) it is remarkable how little is known concerning the role of toxins in endocarditis In rare reported instances of endocarditis in *Klebsiella diphtheriae infections, either there was a supposed bac*teremia with Klebsiella or the endocarditis was caused by secondary invaders from the upper respiratory tract. Investigation of this subject might be fruitful. There are also instances on record of endocarditis in *virus* diseases (*e g.*, smallpox, see Ribbert, Karsner, 1949). Before the discoveries of the causative viruses, such forms of endocarditis were thought to be the result of bacterial toxins There is also a group of endocarditides classified as nonbacterial. Whether some of these may be caused by toxins is difficult to decide.

MECHANISMS OF LOCALIZATION OF VEGETATIONS OF BACTERIAL ENDOCARDITIS

Allen (1939a) made an extensive study of the mode of development of bacterial endocarditis in general, and much of the following is taken from his publications It is possible that a similar mode of localization of the vegetations also holds for subacute bacterial endocarditis. Several views are given in the literature. There are those who maintain that bacteria reach the valve through their blood vessels via the coronary arteries (Coombs, 1909). Thus the pertinent question arises as to whether or not blood vessels are present in normal valves.

Are Blood Vessels Present in Normal Valves? Bayne-Jones (1917) concluded that blood vessels normally occur in the valves of the heart and that his failure to inject them in all hearts was probably caused by imperfect technic and lack of proper conditions He also pointed out that the lateral portions of the semilunar valves are supplied with blood vessels which extend through the commissures, while the central portion of these valves do not disclose blood vessels. In 1921 Gross, in a monograph on the blood supply of the heart, concluded that all fetal valves possess vessels Usually, some time before birth, the blood vessels undergo regression; *in a small percentage of persons, however,* there is a persistence of blood vessels to adult life He believed that this persistence predisposes an individual to embolic valvular endocarditis Kugel and Gross (1925) several years later, on the basis of further examinations, believed that blood vessels exist in some valves in a small percentage of hearts other than those of fetuses, that these are of developmental and not inflammatory origin and that they

occur most frequently in the aortic leaflet of the mitral valve. Such vessels may exist in either a complete or incomplete form.

Ritter, Gross and Kugel (1928) studied 700 human hearts with reference to the existence of blood vessels in the valves. Among these, 14 normal hearts were found which presented blood vessels in some of the valves. They stated that thorough clinical and pathologic examination had failed to reveal that these vessels owe their origin to inflammation In a subsequent study, Gross (1937) reported that blood vessels do not exist in normal valves at all; or if they do, they must be extremely rare. He pointed out that in those instances where blood vessels were present in the heart, widespread stigmas were histologically evident, bearing striking resemblance to those seen in hearts of patients with old rheumatic endocarditis. He believed that an endocarditis of low grade may heal so completely as to leave only blood vessels in its wake. Wearn and associates (1936) found blood vessels in the valves in 86 of 100 hearts of patients who had no history or clinical evidence of endocarditis. They emphasized that 12 of these hearts showed evidence of active or healed valvulitis. Their studies were based on a special method of injecting the coronary blood vessels. Wearn and Moritz (1937) in their study of 235 hearts with no apparent inflammation, found blood vessels in the mitral valve in 50 per cent, in the tricuspid valve in 31 per cent, in the aortic valve in 5 per cent, and in the pulmonic valve in 4 per cent. From this short review it is clear that there still is no agreement as to whether or not blood vessels exist in normal heart valves.

Relation of Blood Vessels to Old Inflammation. From the study of the literature one gains the impression that, rarely, vascularization may occur in either normal valves or valves that were the seat of an inflammation and had healed so completely as to leave practically no evidence of inflammation. Perhaps only those hearts will eventually become involved in endocarditis in which the valves previously had been vascularized, but this possibility has not aroused sufficient interest to make it a subject for study.

The fact that a primary embolus or primary accumulations of bacteria in blood vessels of the valves have never been demonstrated speaks against the embolic theory of acute bacterial endocarditis. Also, since blood vessels were found by Wearn and Moritz (1937) in the tricuspid valve in 31 per cent and in the aortic valve in only 5 per cent, one would expect the tricuspid valve to be more frequently involved by endocarditis than the aortic valve, but of course this is not the case. Besides, as stated above, Gross in his later studies questioned the occurrence of blood vessels in normal valves. There is also no explanation why emboli should be carried principally to the valves of the left side of the heart rather than to the myocardium or mural endocardium.

Role of Trauma and Strain. A favored theory explaining the localization of bacteria on the valves concerns itself with the *formation of eddy currents* in the region of the lines of closure. However, Allen (1939a) pointed out that the sites of eddy currents are the areas between the superior surface of the semilunar valves and the great vessels, and between the ventricular surface of atrioventricular valves and the wall of the ventricle. However, these areas are only exceptionally the seat of primary vegetations. It was also thought that the line of closure of the valves is so often the seat of the vegetations because of the trauma and strain caused by mechanical impingement of the margins against each other. However, Allen tried to show that the trauma from closure, after apposition of the leaflets has taken place, is far less than that produced by edges which have

been slapped together in the manner generally conceived. Therefore, he believes, that the impingement theory seems inapplicable not only for lesions of the normal valve, but also for the great majority of lesions superimposed on diseased valve leaflets, the margins of which are physically unable to impinge on each other.

Experimental Lesions. Nedzel (1936) was able to produce endocardial lesions by the injection of Pitressin with, and sometimes without, subsequent injection of bacteria. He thought that the pressor episode thus brought about causes the valve to exude from its surface a stringy adhesive substance to which bacteria adhere. He believed that during such pressor episodes the margins of the leaflets impinge on each other more forcefully However, as stated above, there is little probability that the theory of impingement *per se* is correct, and besides, acute bacterial endocarditis has been produced in animals after a single injection of virulent bacteria, obviously without the presence of pressor episodes (Blahd *et al.*, 1939)

Local Degeneration. Degenerative changes have been described in deformed valves, giving rise to platelet thrombi which in turn may lead to localization of bacteria (Grant *et al.*, 1927) This is often attributed to local susceptibility because of an acquired altered reactivity of the tissue (Semsroth and Koch, 1930) (See also Chapter VIII on Rheumatic Endocarditis.)

Factors in Localization. Allen (1939a) attempted to elucidate the mechanism of localization by the following explanation which satisfies four universally recognized points. (1) Bacterial endocarditis is often superimposed on a fibroblastic deformity, (2) congenital lesions are particularly susceptible, (3) there is a distinct preponderance of lesions on the left side over those on the right, and (4) bacterial endocarditis is rare in patients with atrial fibrillation secondary to stenosis of the mitral orifice. He believed that a pre-existing valvular fibroblastic deformity often takes the form of a projecting shelf or barrier against which the blood strikes. Because of this obstruction to the systolic discharge, the site of the deformity suffers a great impact; the resulting trauma favors the localization of bacteria. Allen also stated that there seems to be a greater tendency for the virulent rather than the relatively avirulent organisms to invade the right side. Thus the valves of the right side of the heart, though previously not diseased, may become involved in bacterial endocarditis as a result of the presence of highly virulent organisms. He believed that bacteria are prone to localize on the outflow surfaces of the valves because the outflow surfaces of all valves come in contact with a much greater volume of blood and of toxic agents than do the inflow surfaces. Because in atrial fibrillation forcible ejection into the ventricle does not occur, bacteria are not likely to settle on the leaflets of a stenosed mitral orifice. However, the possibility of the influence of other auxiliary factors, he stated, should not be precluded

Evaluation. In spite of Allen's logical discussion, a number of questions still remain unanswered. Why does one encounter, not rarely, bacterial endocarditis developing on normal valves of the left side of the heart? It is possible to produce in experimental dogs acute bacterial endocarditis with a single injection of microorganisms (Blahd *et al.*, 1939). Dick and Schwartz (1946) also recently produced endocarditis in dogs that had no previous injury of the cardiac valves. In regard to the virulence of the organisms, they stated that whereas more virulent strains produce endocarditis in shorter time and with fewer injections than do less virulent strains, it is necessary only to continue the injections with avirulent organisms for a longer time and with increased doses. As will be dis-

cussed later, endocardial pockets and circumscribed areas of endocardial fibrosis projecting into the left ventricle are not particularly rare Such areas are also exposed to the force of the blood stream and pressure Such pockets do occur in instances of older valvular lesions and in acute and subacute bacterial endocarditis. And yet, these pockets or endocardial fibrous plaques are extremely rarely the seat of vegetations. (See case report by Allen, 1941) It seems that all the above-mentioned factors under various circumstances may play a role in the localization of the vegetations Also trauma, produced by abnormally directed columns of the blood stream resulting from congenital anomalies, must be considered. Furlong showed that, in such an instance, vegetations developed not at the site of the congenital defect but at the site of the trauma. Against Allen's (1939b) hypothesis, it must also be argued that atrial fibrillation does occur in acute and subacute bacterial endocarditis with stenosis of the mitral orifice and is definitely not as rare as was previously supposed (de la Chapelle and Graef, 1932, McDonald, 1946). Thus, the argument that forceful contraction of the left atrium is necessary for the production of acute or subacute bacterial endocarditis does not hold. One must also consider the virulence of the agent, the resistance of the host and of the valvular area, perhaps the altered reactivity of the latter, and factors linked with local tissue response. Perhaps too much emphasis is placed on the presence of pre-existing deformities of the valves rather than on whether or not the valves were vascularized prior to the onset of the acute endocarditis. From the evidence at hand (see also Experimental Endocarditis, page 758), there are a number of factors which, in the event of a bacteremia, determine whether or not endocarditis will occur.

Endocarditis Lenta (Subacute Bacterial Endocarditis)

Designation of Endocarditis as Acute and Subacute Forms. Bacterial endocarditis is usually designated as acute bacterial and subacute bacterial endocarditis (endocarditis lenta) This terminology is based on the duration of the disease and is significant from the clinical point of view. Acute bacterial endocarditis generally lasts less than six weeks. In studying a number of reports of acute and subacute bacterial endocarditis, generally no clearcut differences are pointed out between these two forms. There are many transitional forms in which, from the data on hand, no distinction can be made, and it remains often a matter of personal preference whether to classify the endocarditis as acute or subacute. This is, of course, particularly true when acute bacterial endocarditis is superimposed on an old valvular lesion To judge from the literature, it would seem that in some such instances the clinical picture of subacute bacterial endocarditis is more likely to lead to the diagnosis than are the anatomic features. A number of articles and monographs, labelled "bacterial or infective endocarditis," deal with both acute bacterial endocarditis and endocarditis lenta (subacute bacterial endocarditis). It is confusing when in such communications the results of bacterial studies, the age incidence, the duration of the disease, and the gross anatomic and histologic findings of both types of endocarditis are discussed under one heading. This would be justified if acute bacterial endocarditis were an early stage of a later-developing endocarditis lenta. The point in question is whether acute bacterial endocarditis is one entity and subacute bacterial endocarditis a different, well-defined entity or disease. Are

acute and subacute bacterial endocarditis two diseases? Does subacute bacterial endocarditis or endocarditis lenta start as acute bacterial endocarditis? Is it possible from the gross and histologic picture alone to distinguish between acute bacterial and subacute bacterial endocarditis? Knoll (1941) pointed out the difficulties of classifying anatomic lesions under the heading of subacute bacterial endocarditis (endocarditis lenta) in the light of expert opinion and recent experimental work

Before a discussion of these questions is undertaken, a few data in regard to age distribution, involvement of various valves, and a description of the gross and microscopic appearance of endocarditis lenta will be given

Age Incidence. The age distribution of endocarditis lenta was given by White (1944) from a study of 250 cases as follows six patients were under 10 years of age, 42 between 10 and 20, 79 between 20 and 30, 53 between 30 and 40, 39 between 40 and 50, 21 between 50 and 60, and 10 over 60 White also stated that the youngest patients on record were one and one-half years, two and one-half, and five years old He remarked that this disease is very rare in young children In Seabury's (1947) series of endocarditis lenta, 55 8 per cent of the patients were found to be in the third and fourth decades Libman and Friedberg (1948) stated that two-thirds of their patients with endocarditis lenta were between 20 and 40 years old. In the report of Clawson (1941), 514 cases of bacterial endocarditis were encountered among 30,265 autopsies with 364 instances of endocarditis lenta in which symptoms had lasted more than six weeks. There were 237 males and 127 females. The following age distribution was found. There were six patients in the first decade, 35 in the second, 83 in the third, 81 in the fourth, 71 in the fifth, 48 in the sixth, 33 in the seventh, four in the eighth, and three patients in the ninth decade. Zeman (1945) found endocarditis lenta in eight patients whose ages were between 60 and 87 years.

Valves Involved. Table IX-7 presents the frequency of involvement of the various valves and of the mural endocardium in Denman's (1942) series of 50 cases. (One of Denman's cases is not included since apparently only the epicardium was involved)

TABLE IX-7

Frequency of Involvement of Valves and Mural Endocardium in 50 Patients with Endocarditis Lenta (Denman, 1942)

Valves and/or Mural Endocardium	*No of Hearts Affected*
Mitral	21
Aortic	10
Pulmonic	1
Tricuspid	1
Mural endocardium	2
Mitral, aortic and tricuspid	1
Mitral and aortic	3
Mitral and tricuspid	2
Mitral and mural endocardium	4
Aortic and tricuspid	2
Mitral, aortic and mural endocardium	1
Aortic and mural endocardium	1

TABLE IX-8

Organisms Recovered on Blood Culture from 157 Patients with Subacute Bacterial Endocarditis (Seabury, 1947)

Organisms	*Number*	*Per Cent*
Streptococcus viridans (alpha)	126	80.2
Streptococcus hemolyticus (beta)	3	1 9
Streptococcus anhemolyticus (gamma)	12	7 6
Gram-positive cocci in chains	3	1 9
Gaffkya tetragena micrococcus tetragena	1	0 6
Gram-negative pleomorphic rods	1	0 6
Staphylococcus albus	1	0 6
Staphylococcus aureus	1	0 6
Brucella abortus	1	0 6
Clostridium	1	0 6
Absent in life, present at autopsy	7	4 5

Among 1000 consecutive autopsies performed at Michael Reese Hospital on patients over two years of age, endocarditis lenta was encountered 15 times. The mitral valve alone was involved three times, the aortic valve five times, and both valves seven times.



Figure IX-12 Endocarditis lenta Streptococci in superficial portion of vegetation

Causative Organisms. In the vast majority of cases *Streptococcus viridans* was found to be the causative agent (Figure IX-12) Moore (1944) found this organism in 81 per cent of his cases. Table IX-8 lists the organisms recovered by Seabury (1947) on blood culture from 157 patients with endocarditis lenta. Libman and Friedberg (1948) mentioned among other causative organisms members of the genus Neisseria, such as *Neisseria sicca (Diplococcus pharyngis siccus)* and *N. catarrhalis,* as well as corynebacteria, *Spirillum surati, Streptobacillus moniliformis* and others It may be mentioned here that Jones (1950) reviewed the literature from 1936 to 1948, inclusive, of cases of subacute bacterial endocarditis of nonstreptococcic etiology. Rarely has endocarditis lenta been reported to have been caused by *Klebsiella pneumoniae* (Friedlander's bacillus). Thayer (1931) mentioned only one such infection Bacteria, however, are not always demonstrable in certain clinically clear-cut cases of endocarditis lenta, either post mortem or during the course of the disease, although they had been previously recovered in blood cultures and no specific treatment had been given. Libman (1913) accordingly subdivided endocarditis lenta into a bacterial and an abacterial stage. No organisms are present in the latter stage in the blood stream or in the vegetations. In the abacterial stage, the patient may succumb to renal insufficiency or to the effects of embolism. Libman and Friedberg believed that bacterial cultures are negative in the so-called free stage because bacteria are then no longer present on the surface of the endocardial vegetations and, therefore, none appear in the blood stream. However, it is also likely that abundant antibodies in the blood stream may cause bacteria to be precipitated, so that they may localize on the cardiac valve. It has often been maintained that patients with bacterial endocarditis possess various immune bodies which are able to destroy the organisms. Only if bacteria enter the circulating blood faster than immune bodies can destroy them, may they be demonstrable in blood cultures.

Portal of Entry. Weiss (1934) pointed out that the portal of entry of the bacteria in endocarditis lenta is most often the upper respiratory tract. However, endocarditis lenta, like acute bacterial endocarditis, has also been reported in association with a number of diseases. Not rarely this disease has been observed following dental extraction. Of 92 instances of endocarditis lenta reviewed by Barnfield (1945), in six extraction of teeth was associated with the disease A study of these instances suggested that extraction either may have caused endocarditis lenta or, in those cases in which extraction had been performed after the onset of the endocarditis, may merely have been the apparent cause of the infection. He concluded that there is evidence that post-extraction bacteremia causes endocarditis lenta.

The most frequently associated or preceding disease is rheumatic fever. This will be discussed subsequently.

Distinction from Acute Bacterial Endocarditis and Description. In some cases, clear-cut gross distinction between acute bacterial endocarditis and endocarditis lenta (subacute bacterial endocarditis) can be made with relative ease. The diagnosis of acute bacterial endocarditis is

not difficult if the recent vegetation is massive and if it is imposed upon a valve which shows no evidences of older inflammation, in other words, if the valve is tender and delicate. As pointed out previously, the vegetations may also be present on the adjacent mural endocardium and large ulcers are not rare. It seems obvious that such an endocarditis must be designated as acute vegetative endocarditis and, because of the presence of bacteria which invariably are easily demonstrated, as acute bacterial endocarditis. If engrafted upon an old endocarditis, the latter shows evidence *of old scarring with retraction* of the cusp, or adhesions between the cusps. In typical endocarditis lenta, the vegetations are also large but not massive and their coloration contains more gray or yellow than red They are often vermiform in appearance The endocarditis often extends beyond the limits of the leaflets and the mural endocardium is invariably involved. Minute ulcerations, never large ones, are present in adjacent free margins of thickened leaflets, giving them a moth-eaten appearance Tearing of the involved valves may occur The cusps or leaflets always show evidence of older lesions, most commonly an old endocarditis These older lesions may be *characterized* only by slightly thickened free margins of the cusps, or rolled edges or moderate retraction of the cusps Occasionally, adhesions of a slight degree may be found between the cusps Old healed lesions with marked fibrosis, hyalinization *and calcification are* usually not present Parietal lesions occur predominately in the left atrium and left ventricle. Fibrous irregularities as a result of healing often assume a characteristic coarse "sharkskin" appearance. The organism present in the vast *majority of cases of endocarditis* lenta is *Streptococcus viridans*, probably of a special type (see page 737). The histologic finding of many cocci in the valves is not sufficient for diagnosis From a practical point of view it may be wise to remember that if a *majority of the following factors* are present it is more likely that the case in question is one of an endocarditis lenta *rather than acute* bacterial endocarditis: (1) evidence of an older endocarditis, not of old calcific changes; (2) long vermiform vegetations and small ones, side by side; (3) minute ulcers, "moth-eaten" free edges of the cusps, (4) involvement of the mural endocardium, and (5) presence of *Streptococcus viridans*, probably of a special variety. Stricter criteria will be offered subsequently.

Microscopic Changes. Jaffé (1932) gave an extensive description of the histologic changes in the valves of endocarditis lenta The vegetations usually *consist of fibrin*, platelets and polymorphonuclear leukocytes, the masses of fibrin being most pronounced *on the surface* of the vegetations. Minute foci of calcification are not rare. Though Jaffé believed that the cocci *per se* became calcified, recent studies of healing endocarditis make it seem more likely that lime is deposited within the necrotic portions of the vegetations, close to their edges. Necrotic portions of the valve leaflets are found adjacent to large or small areas of inflammation. Often, large cells are noted with one or several round nuclei, and oval or slightly spindle-shaped cells, the long axis of which is directed toward *the necrotic portion. Lymphocytes, histiocytes*, pigment-laden phagocytes and occasional plasma cells are also evident. These cells are found within an *edematous fibrillar* ground substance which is traversed by many capillaries.

Early microscopic changes. While the above histologic picture is seen in advanced cases, Jaffé believed that initially there is a swelling of the endothelial cells close to the line of closure The nuclei soon disappear and the cells become necrotic. At about this time there appear, in the subendocardial layers, oval cells with vesicular

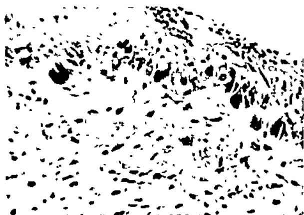


Figure IX-13 Section of vegetation in endocarditis lenta Note palisading of large histiocytic cells, many with multiple nuclei. Hematoxylin and eosin. X 250

nuclei, these cells often assuming palisade formations with their long axis perpendicular to the free margins of the valves. These cells soon become necrotic and gradually fuse with the platelets of a thrombus which had formed in that region The palisading of cells is characteristic (Figure IX-13) and is always demonstrable if enough sections are studied. Jaffé thought that these cells are young connective tissue cells (fibrocytes). Circumscribed, nodular, cellular infiltrations, consisting of portions of the loose edematous ground substance and a number of cells with round nuclei and much cytoplasm are also found early Giant cells are often seen, particularly at the surface of these small nodules. Sometimes these giant cells resemble Langhans giant cells, with nuclei arranged at the periphery of the cytoplasm. Jaffé thought them to be either fused histiocytes or fibrocytes

Giant Cells and Necrotic Areas. Giant cells are also encountered at the marginal portion of the inflamed leaflets and within the necrotic parts of the vegetations or valves (Figure IX-14). Those at the former site seem to arise by fusion of several lining endothelial cells of the valve. Their nuclei and the nuclei of more or less intact, but swollen, endothelial lining cells are morphologically identical. Also the fact that they are found close to the endocardial lining is probably significant. The giant cells of the necrotic foci within the vegetations generally seem to be of the foreign-body type. It has been mentioned that calcium is often deposited early within the necrotic portion of the valve or vegetation (Figure IX-15). From a study of healing forms of endocarditis lenta (*q v.* for reference), it appears that giant cells of foreign-body type are not rarely found ad-



phonuclear leukocytes Hematoxylin and eosin X 105 (Courtesy of Armed Forces Institute of Pathology, Acc. No 37488-1)



Hematoxylin and eosin. X 110.

jacent to such lime deposits. Eventually necrosis occurs within the nodules described above The necrosis starts at the periphery of the nodules and extends outside the nodule into the valvular tissue. Cocci which are usually present at the periphery do not extend into the necrotic portion of the nodule. Gradually evidence of suppuration appears, often with necrosis and severe destruction of the tissues At the periphery of the necrosis, fibrocytes and histiocytes accumulate and these gradually extend into the necrotic portion, after which there is new formation of capillaries and attempts at scarring or healing (Figure IX-16). The areas of necrosis may extend from the center of some of the nodules to the periphery, with perforation of the valvular endocardium and with formation of ulcers and thrombi

Differences from Acute Bacterial Endocarditis. In comparing this description with the histologic changes in valves with acute bacterial endocarditis several important differences are evident In acute endocarditis, exudation is much more pronounced, large areas of necrosis of the valve intermingled with polymorphonuclear leukocytes are sloughed, and large deep ulcers occur. In endocarditis lenta, *ulcers are small and more superficial* Evidence of repair with newly formed



Figure IX-17 Vegetation of endocarditis lenta Note palisading of histiocytes bordering a necrotic portion of mitral valve Hematoxylin and eosin X 150



Figure IX-18 Calcification of distal portion of vegetation of endocarditis lenta Hematoxylin and eosin X 75



Figure IX-16 Young scar tissue in healing vegetation of endocarditis lenta Hematoxylin and eosin X 150.

connective tissue cells and actual granulation tissue is rarely seen in acute bacterial endocarditis, but is always present in endocarditis lenta. Jaffé emphasized that the formation of nodules containing giant cells, as described above, does not occur in acute bacterial endocarditis, but is pathognomonic of endocarditis lenta Palisading cells are almost always encountered in endocarditis lenta (Figure IX-17). Sometimes they are also found early in acute bacterial endocarditis but here they soon become involved in the necrotizing process Thus from the gross description and from the microscopic details (Figure IX-18) it must be concluded that there exists a type of bacterial endocarditis,

called endocarditis lenta, which differs not only in its clinical manifestations, but also in some anatomic respects from acute endocarditis that is superimposed upon an old endocarditis. However, it must be pointed out at once that not all cases classified and reported as endocarditis lenta conform to the above description.

Endocarditis Lenta as a Special Entity. Libman and Friedberg (1948) repeatedly stated that acute bacterial endocarditis and endocarditis lenta are sharply distinguishable both as to their causation, and their clinical and pathologic features Schottmuller (1910) maintained that endocarditis lenta is an entirely separate entity, a specific disease caused by *Streptococcus viridans*. One of the clinical characteristics of the disease is its slow protracted course. For this reason he called it endocarditis lenta ("lenta" meaning slow or insidious) Karsner (1931) stated that endocarditis lenta in its typical form is characteristic It is not literally subacute but represents a more or less continuous formation of acute or subacute verrucous and vegetative endocarditis in close association with progressive chronic endocarditis and granulation tissue. The acute process does not ordinarily have large vegetations nor is it always free from large masses of thrombi Pedunculated vegetations are rare. As Jaffé has shown, the microscopic picture of endocarditis lenta is characteristic.

From the clinical data, the gross, microscopic and bacteriologic findings and the relevant literature, the following facts are elicited: (1) Endocarditis lenta is a definite clinical entity, differing from acute bacterial endocarditis and uncomplicated sepsis; (2) the gross appearance of the involved valve is quite characteristic and the microscopic appearance perhaps even more characteristic; (3) *Streptococcus viridans* is reported to be present in the vast majority of instances, as will be



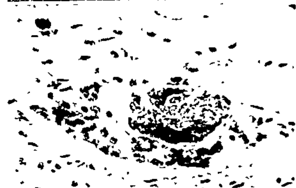




Figure IX-19. Dark amorphous material surrounded by a foreign-body giant cell within the myocardium Hematoxylin and eosin. X 580

Figure IX-20 Calcific material surrounded by foreign-body giant cells Van Gieson X 380

Figure IX-21 Foreign-body granuloma with calcium deposits in the center Hematoxylin and eosin X 150 These foreign-body granulomas are interpreted as evidence of healing of the subacute bacterial endocarditis.

Figures IX-19 to 21 are reproduced by courtesy of Archives of Pathology from article by the author (*Arch. Path*, 42 574, 1946).

pointed out later; (4) in a high percentage of cases there is either a history of rheumatic fever or Aschoff bodies are present in the myocardium; (5) whereas it is not difficult to produce acute bacterial endocarditis experimentally, it is questionable if endocarditis lenta has ever been produced in an experimental animal.

Libman and Friedberg discussed at length the characteristic clinical picture which Libman over a period of many years had so amply described, in fact, the term "Libman's disease" (not to be confused with Libman-Sacks disease) is sometimes used for this clinical entity

The main gross and histologic differences between acute bacterial and endocarditis lenta have been pointed out above. Jaffé felt certain that the histologic features were characteristic. It is also worth mentioning that several investigators have been impressed by the occurrence of hyperplasia of the reticulo-endothelial system in this disease Istamanowa (1928) emphasized that in 30 instances of endocarditis lenta there was hyperplasia of the cells of the reticulo-endothelial system, affecting the lymph nodes, spleen, liver and bone marrow Such hyperplasia was not present in patients with old valvular disease. However, she did not think that this reticulum cell hyperplasia differs from that seen in other infectious diseases Jaffé was also impressed with the reticulum cell hyperplasia in endocarditis lenta.

Held and Lieberson (1943) stated that endocarditis lenta represents a state of high local and general tissue immunity to bacterial invasion They further emphasized that the immunity resides in the local endothelial structures, as well as in the general reticulo-endothelial system. Since the reaction to this bacterial invasion is largely endothelial, they thought that the disease may rightfully be termed "infectious endotheliosis"

ROLE OF *Streptococcus viridans*

It has often been stated that *Str. viridans* is less virulent than other streptococci and, therefore, may cause the slowly developing endocarditis of endocarditis lenta. On the other hand, older investigators believed that there are particular types of green streptococci which have a special affinity for the heart valves and cause endocarditis lenta. Karsner does not believe in such an elective localization. Wheeler and Foley's (1945) studies are noteworthy They isolated streptococci from 17 instances of endocarditis lenta. They found that most of these were serologically identical and frequently belonged to the Lancefield Group D. They also stated that the bacteriologic methods employed in the identification of "alpha" or "green-producing" streptococci usually indicate nothing concerning the exact identity of the strain. Interestingly enough, Wheeler and Foley emphasized that enterococci (*Str fecalis*), also occasionally encountered in endocarditis lenta, are serologically identical and often belong to the Lancefield Group D Also, Skinner and Edwards (1942) recorded two instances of endocarditis lenta caused by an enterococcus. Both strains were identified as members of Group D of the Lancefield classification of streptococci. From this study one becomes more and more inclined to believe that organisms of the Lancefield Group D are perhaps the ones which cause endocarditis lenta, provided other suitable conditions are present within the heart valves

Relationship of Endocarditis Lenta to Rheumatic Fever. Much has been written about the relationship of endocarditis lenta to rheumatic endocarditis (See also Rheumatic Endocarditis.) Whatever this relationship may be, relevant studies have been undertaken because of the fact that so often patients with endocarditis lenta

give a history of one or several attacks of acute rheumatic fever. For the purpose of the following discussion, neither the clinical histories of such patients, nor the histologic changes of the valves, nor so-called "rheumatic stigmata" will serve to indicate that the patient had had rheumatic fever, but rather, only the one indisputable evidence of rheumatic heart disease, the *myocardial Aschoff body* From the recent literature (see MacIlwaine, 1945), it becomes increasingly apparent that the more carefully the myocardium is examined in instances of endocarditis lenta, the more frequently are Aschoff bodies encountered As a matter of fact, it appears that Aschoff bodies would be demonstrable in many more hearts with endocarditis lenta if a greater number of blocks from the myocardium were examined In a study of sections of the myocardium of 10 children with endocarditis lenta, Saphir and Wile (1933) found Aschoff bodies in every heart This constant finding of Aschoff bodies in the myocardium of children having endocarditis lenta is partly explained by the relatively larger portions of the myocardium that were studied from the hearts of children than are usually studied in adults; and partly because the interval between rheumatic fever and endocarditis lenta is usually shorter in children than in adults. Table IX-9 presents data accumulated by MacIlwaine to show the percentages of Aschoff bodies found in the myocardium of hearts with endocarditis lenta by various investigators. If the finding of the Aschoff body is taken as the only criterion for rheumatic heart disease it becomes immediately obvious that careful studies of the myocardium indicate that a great many patients with endocarditis lenta must have had rheumatic myocarditis and, in all likelihood, also rheumatic endocarditis.

TABLE IX-9

Incidence of Aschoff Bodies Found in Endocarditis Lenta, in Various Published Series (MacIlwaine, 1945)

Authors	*Number of Cases Endocarditis Lenta*	*Percentage with Aschoff Bodies*
Clawson and Bell (1926)	61	11.5
Gross and Fried (1937)	30	30 0
Buchbinder and Saphir (1939)	40	37 5
Saphir (1935)	35	40.0
Clawson (1929)	60	45 0
Von Glahn and Pappenheimer (1935)	26	46 0
MacIlwaine (1945)	34	85 3
Saphir and Wile (1933)	10	100 0

Streptococcus viridans **and Rheumatic Valvulitis.** There can be no doubt of the role of the *Str. viridans* in endocarditis lenta. It also becomes more and more apparent that it is the *Str viridans* Lancefield Group D which, if carefully looked for, may perhaps be identified as the specific organism The difficulty lies in explaining why the *Str. viridans* (Lancefield D), superimposed upon rheumatic valvulitis, produces the gross and histologic picture of endocarditis lenta and the insidious clinical feature of the disease There are those who explain both the ensuing anatomic changes and the clinical picture on the altered reaction of the previously inflamed valve, the original infection having produced the hyperergic inflammation and the final infection causing the immune reaction, *i e.*, endocarditis lenta. The supporters of this hypothesis assume, of course, that both diseases have the same causative agent, the difference in the disease lying in the difference of the reaction of the host. The arguments against this hypothesis, attractive though it may be, are many and have been mentioned previously (see Rheumatic Endocarditis). It must be maintained that at present this hypothesis has not been proven. The only proof for it lies in the experimental production of both rheumatic fever and endocarditis lenta with the same organism This requires, not only the experimental production of rheumatic endocarditis *per se*,

but also the production of that most characteristic entity, an *unequivocal* Aschoff body. Although even in the recent literature (McKeown, 1947) the assumption is made that Aschoff bodies have been produced experimentally, a critical review and analysis of the accompanying illustrations disclose that the lesion in question, though *resembling Aschoff bodies,* should not be so designated In my opinion, typical Aschoff bodies have not been produced experimentally up to the present time It also should be emphasized that in many of the relevant experimental researches (see Rheumatic Fever) the organisms *used were identified* merely as *Str viridans* and were not further classified It may be fruitful to repeat a number of these experiments, using only the Lancefield D type and its products Also, if in the future streptococci are isolated from patients with rheumatic fever, it would seem *imperative to* determine whether or not they may be classified as belonging to Lancefield Group D

Relationship of Endocarditis Lenta to Valvular Disease. Clawson and Bell (1926) thought that endocarditis lenta is determined by factors of virulence and resistance, and *that it differs only* in degree from other forms of endocarditis. On the other hand, Von Glahn and Pappenheimer (1935) concluded *that endocarditis* lenta is a new infection superimposed on an unhealed rheumatic endocarditis There are other suggested possibilities why *Str. viridans* produces the *histologic* picture of endocarditis lenta *if* engrafted upon a rheumatic valvulitis Saphir *and Wile (1933) emphasized* that the finding of *typical Aschoff bodies in the myocardium in cases* of endocarditis lenta may be proof *that the endocarditis* is not an immune response in a previously *hypersensitive* patient. They maintained that it would be difficult to explain the simultaneous response of a tissue in two different ways, *i e*, exhibition of both a hypersensitive reaction of which the Aschoff body *is an example,* and an immune reaction of which *the vegetation* of endocarditis lenta is an example. They stated that, because *of the* rheumatic valvulitis, a subsequent localization of bacteria is somehow *facilitated.* Gross and Fried (1937) believed that *some* of the cases *of* acute *and subacute* bacterial endocarditis were "thrown *into activity" by the* superimposed *bacterial* infection rather than that the activity *of the rheumatic process* predisposed to the bacterial endocarditis *MacIlwaine* (1947) believed that the acute changes seen in *rheumatic* endocarditis are such as to offer a focus for the localization of bacteria from the circulating blood. In endocarditis lenta the organisms are relatively avirulent and require for their implantation some localizing factor in the valves themselves It is suggested that such a factor is the presence of acute rheumatic lesions and that these are the determining pathogenic factors in the majority of cases of endocarditis lenta

Postulates for Specific Criteria of Endocarditis Lenta. Thus, three facts appear to stand out: (1) There is a characteristic clinical picture in endocarditis lenta, (2) the Lancefield strain D of *Streptococcus viridans* is the offending organism, and (3) if carefully sought, Aschoff bodies, the only definite histologic criterion of rheumatic heart disease, are often found in the myocardium. The question must be raised *immediately whether* or not the last two factors will be found regularly in carefully studied cases Perhaps it may be going to extremes of precision to *recommend,* according to our present knowledge, that endocarditis lenta be *diagnosed* anatomically, not *only* on *the basis of the fairly* characteristic gross and histologic picture of the valves, *but also, if evidence* of rheumatic endocarditis is brought for-

ward, by the detection of Aschoff bodies. Bacteriologically, *Str viridans*, Lancefield Type D, should be demonstrated. If this is done and these criteria are established, endocarditis lenta will become a much more precise entity, not only clinically, which it is already considered to be by many, but also bacteriologically and pathologically Perhaps it may then become recognized as a specific disease.

The *objections* to such strict criteria are immediately obvious. There are cases on record of endocarditis lenta in which organisms other than streptococci were demonstrable Besides, there are many reports of endocarditis lenta engrafted upon congenital defects in the heart and upon syphilitic aortic valves. There are also acute bacterial (streptococcal) endocarditides which are superimposed on old inflammatory valvular lesions These definitely are not instances of endocarditis lenta, and yet the old inflammation of the valve is often considered to be of rheumatic origin. Endocarditis lenta caused by *organisms other than Streptococcus viridans* is comparatively rare Cases of this type should always be re-studied carefully bacteriologically to see if, in addition to the bacterium first discovered, another might also be present. MacLean and Howell (1947) showed that in a case of endocarditis lenta two types of streptococci were present, one of which had become sensitive to penicillin It has previously been pointed out that Wheeler and Foley (1945) demonstrated that certain enterococci which were encountered in endocarditis lenta were serologically identical and often belonged to Lancefield Group D, that a gross anatomic diagnosis of endocarditis lenta alone is often insufficient, and that a careful microscopic examination of the valvular lesions is essential to verify the diagnosis. In many reports of endocarditis lenta, the diagnosis has been made only on the basis of the clinical or of the clinical and gross anatomic findings and has not been supplemented by microscopic studies. The same criticism may be made of many reports of endocarditis lenta engrafted on either congenital cardiac defects or syphilitic aortic valves. In most of these instances, the diagnosis of endocarditis lenta had been made principally on the findings of *Str. viridans.* In retrospect, many of these cases seem to be instances of acute bacterial endocarditis engrafted upon old valvular defects. Again, it must be emphasized that the demonstration of *Str. viridans per se* is not sufficient to make a diagnosis of endocarditis lenta

Koletsky's (1942) observations lend no support to the belief that *syphilis* is a significant predisposing factor in the development of endocarditis lenta. He studied 5 cases of combined syphilitic heart disease and bacterial endocarditis among 4000 consecutive autopsies. In 2 there was syphilitic aortitis alone and in 3 there was involvement of the aortic valve. He did not believe that any significance could be attached to the syphilitic lesion as a precursor of the endocarditis, since stigmata of rheumatic fever were demonstrated in 4 cases, and in at least 2 of these there were syphilitic and rheumatic lesions of the aortic valve. In the fifth case, syphilis was confined to the root of the aorta and an acute bacterial endocarditis was apparently imposed upon a normal aortic valve

Acute Bacterial Endocarditis and Old Endocarditis. There are also cases on record of acute bacterial endocarditis caused by streptococci, superimposed on old valvular lesions which were interpreted as of rheumatic origin. Neither the clinical picture nor the gross picture was characteristic of endocarditis lenta. In that respect it must again be emphasized that acute bacterial endocarditis, which for some reason was not severe enough to cause death, may heal with the formation of scar tissue

on the valve. As a matter of fact, there is no reason whatever, as will be discussed later, why an old mitral or aortic endocarditis must always be labelled old "rheumatic endocarditis" rather than old "nonspecific" endocarditis. It seems obvious that acute bacterial endocarditis may undergo healing and that such a nonspecific inflammatory process eventually will come to a standstill The result will be a deformity of the valve. Thus, if there are no definite indications that such old valvular lesions are rheumatic in origin, a rheumatic etiologly should not be assumed. Such an instance of acute and old endocarditis should be classified as acute bacterial *(Str. viridans)* endocarditis superimposed on an old (nonspecific) endocarditis and not as endocarditis lenta, simply because of the findings of *Str. viridans*, recent vegetations and an old endocarditis. Again it must be emphasized that the finding of *Str viridans* does not mean that the acute valvular lesion should be classified as endocarditis lenta MacIlwaine reported 12 cases of bacterial endocarditis in 7 of which Aschoff bodies were present in the myocardium. However, there is no evidence that these 7 instances were caused by *Str. viridans* Lancefield Group D. In other words not every acute endocarditis caused by any type of organism, superimposed upon a rheumatic endocarditis, should be considered as endocarditis lenta

Characteristics of Endocarditis Lenta. From the foregoing, it can now be stated that it is definitely possible from the gross and histologic appearances to distinguish between acute bacterial endocarditis and endocarditis lenta These are different diseases. Endocarditis lenta (subacute bacterial endocarditis) does not start as an acute bacterial endocarditis, in that respect, the term subacute bacterial endocarditis is a misnomer. Endocarditis lenta is characterized by (1) a characteristic clinical picture, (2) characteristic gross and microscopic features, (3) presence of *Str. viridans*, Lancefield D strain, and (4) presence of definite evidence of rheumatic endocarditis, preferably Aschoff bodies in the myocardium. As has been stated before, the changes in the valves in endocarditis lenta seem to be gradually progressive, with foci of attempted healing combined with foci of progressive inflammation. Such progressive changes are reminiscent of the changes in the kidneys *in the stage between acute and subacute* glomerulonephritis. Here the patient is seemingly well clinically, but after a long interval he may manifest symptoms of subacute or even chronic glomerulonephritis There seems to be, in both these instances, a smoldering and gradually progressing inflammation Just what takes place in the valves and kidneys, in these respective conditions, in the interval and just why the inflammation smolders and progresses in such a peculiar way is not known.

Nomenclature. It is perfectly clear that "subacute bacterial endocarditis" is not a correct term, since the disease is not just a subacute inflammation There are a number of other terms used for subacute bacterial endocarditis, such as malignant endocarditis, chronic infectious or chronic septic endocarditis, and endocarditis lenta. Schottmuller (1910) used the term "endocarditis lenta" and thought that this was a specific disease due to *Str viridans*. Libman and Friedberg objected to this term because they believed subacute bacterial endocarditis might be caused by various organisms and not by *Str. viridans* alone. Karsner (1931) favors the term endocarditis lenta, meaning slow endocarditis, which expresses both the clinical course and the anatomic nature of the disease. In view of the above concepts, it is evident that the term "subacute bacterial endocarditis" is misleading. For want



Figure IX-22 Healing vegetations in endocarditis lenta of mitral valve, following treatment with penicillin (WCGH, 50 A 29)

of a better term, the designation *endocarditis lenta* is recommended.

Histologic Changes in Endocarditis Lenta as Result of Treatment (Penicillin). There are a number of histologic studies available of the appearance of the valvular lesions following penicillin treatment (Figure IX-22). Most of these studies are based on a comparison between changes of the valves as described in the literature in untreated instances or as observed in untreated control cases, and those encountered in the valves of treated cases It must be mentioned, however, that as Karsner and Lund (1948) stated, this is not a precise evaluation; for interpretation of changes following penicillin therapy is difficult because variable degrees of fibrosis and fibrin formation are formed in untreated cases. Moore (1946) stated that penicillin in endocarditis lenta promotes healing but that the basic processes of healing are not modified. These processes are as follows: covering of the exposed surface of the vegetation with fibrous tissue, invasion of the layer of colonies of bacteria, phagocytosis of bacteria, calcification of bacterial colonies, hyalinization and calcification of the central core of the vegetation and endothelization of the spaces and clefts in the vegetation. Moore believed that in some patients healing is accompanied by excessive calcification and that the result may be calcific stenosis of the valve.

Carnes and Tinsley (1946) described grossly small calcified nodules, small flat granular vegetations, fibrous thickenings and fusion between cusps. In two of their five cases which they classified as showing evidence of healing, perforations of the cusps were noted. No mention is made as to whether the perforation occurred in a healing cusp, or was located where ulcerative and vegetative endocarditis was still present. In the microscopic examination, they were impressed with a few focal areas of leukocytic infiltrations and with calcific nodules that still contained gram-positive cocci. Also encountered were basophilic nuclear debris and an infiltration of mononuclear and multinuclear cells. Two other

instances, seemingly presenting more advanced healing, disclosed a relatively acellular connective tissue in which large masses of coarse calcific material were embedded but in which no bacteria, necrosis or leukocytic infiltrations were seen. Hildebrand and Priest (1947) reported 34 instances of penicillin-treated endocarditis lenta The lesions at autopsy were small and firm, and calcification sometimes was marked. Healed valvular lesions resembled healed stages of rheumatic valvulitis. Polymorphonuclears were frequently noted and fibrin seemed to persist. Geiger and Durlacher (1947) found pale, dark and smoothly-endothelialized masses of connective tissues and areas of calcification, but no bacteria

The histologic criteria of healing are given in Table IX-10.

TABLE IX-10

Histologic Criteria of Healing, According to Jones and Associates (1947)

Stage 1 Indistinguishable from vegetations of untreated cases, active inflammation

Stage 2 Much organization, slight or no inflammatory reaction, intermediate between stages 1 and 3

Stage 3 Organization advanced, lesion probably nearly healed.

Feature	*Stage 1*	*Stage 2*	*Stage 3*
Polymorphonuclear leukocytes in vegetation or valve	Moderate number	Few or none	None
Mononuclear cells in vegetation	Some	Some	Few or none
Growth of endothelial cells over vegetation	Never	Never	Often
Newly formed fibrous tissue	Little	*Much, cellular*	Variable amount
Organisms	Yes	Yes	Sometimes
Positive culture from vegetation	Sometimes	Never	Never

Jones and associates (1947) pointed out that in untreated bacterial endocarditis, although acute inflammatory changes are always present in some part of the lesion, there may also be areas of healing In assessing healing in these cases, it is necessary to examine several sections from each vegetation and to form an opinion for the *composite picture.*

There are other evidences of healing of endocarditis lenta Saphir and Leroy (1948) have reported *true aneurysms* of the mitral valve (Figures IX-23 and IX-24) These aneurysms are outpouchings of portions of valves in the absence of vegetations or ulcerations Grossly these aneurysms resembled on superficial examination broad-based, healed vegetations covered by the endocardium. They were obviously the result of a circumscribed valvulitis with consequent granulation tissue and young scars which, because of intracardiac pressure, formed saccular outpouchings. All these aneurysms were covered by valvular endothelium. It is interesting that Carnes and Tinsley (1946) also mention aneurysms in their studies of healing bacterial endocarditis However, they did not state whether the aneurysms were mycotic (false aneurysms) or true aneurysms of the type reported by Saphir and Leroy It has been emphasized repeatedly that *calcification* within the vegetation is regarded as evidence of healing. Saphir (1946) found small calcific emboli in the myocardium of patients with endocarditis lenta (Figures IX-19 to 21) these patients had been treated with sulfonamide compounds and penicillin and their hearts presented healing vegetations of the aortic valves. Such calcific emboli had caused typical foreign-body granulomas within the myocardium. It was emphasized that granulation tissue occurs

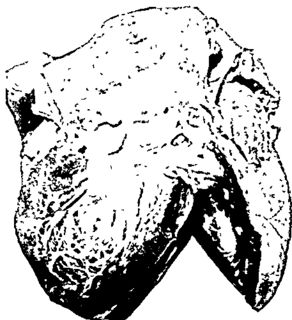


Figure IX-23. Aneurysm of anterior leaflet of mitral valve following treatment of endocarditis lenta with penicillin (WCGH, 45 A 429)

at the base of the vegetation while calcium is deposited at the periphery of the vegetation within the necrotic masses Obviously such calcium particles can break off easily and may lodge in branches of coronary arteries, causing foreign-body granulomas. These findings were considered as characteristic evidences of healing of endocarditis lenta. As has been stated previously, calcification of vegetations also occurs and has been observed in untreated instances of acute endocarditis and endocarditis lenta. Cullinan and Baxter (1930) reported an instance of pneumococcal endocarditis in which they stressed the great rapidity (23 *days) with which calcification took place* in newly formed vegetations. It is interesting that there were also calcareous emboli in the kidneys.

COMPLICATIONS AND SEQUELAE OF ACUTE BACTERIAL ENDOCARDITIS AND ENDOCARDITIS LENTA

The sequelae of acute bacterial endocarditis and endocarditis lenta may be divided into those occurring as the result of the septicemia *per se,* those resulting from embolism, and those occurring in the heart itself as a direct result of the vegetative endocarditis. The last will be discussed first.

CARDIAC COMPLICATIONS

Mural Endocarditis. Mural endocarditis occurring as a complication of valvular endocarditis has been discussed previously. Also the occurrence and mechanisms of



Figure IX-24 Healing endocarditis lenta of mitral valve. Note, in center, recent aneurysm of leaflet; to its left, healing vegetation, and below, endocardial thickenings with early formation of pockets which open toward apex of heart.

erosive mycotic aneurysms have been described. Levy and Hull (1947) reported such an apparently true aneurysm which was healing, situated in the interventricular septum. It had perforated into the right ventricle.

Myocardial Changes in Acute Bacterial Endocarditis and Endocarditis Lenta. Various *degenerative changes* in the myocardium, resulting from the underlying acute infectious disease, have been described; among these are cloudy swelling and fatty degeneration. Grossly, the myocardium is *almost invariably softer than normal*, its cut surface having a cooked appearance, and its architecture being obscured. In addition to these degenerative changes one often observes gray or yellowish streaks in the myocardium, which are clearly seen through the intact endocardium. On section of the myocardium, there are also encountered occasional reddish foci of minute *hemorrhages* and yellowish areas surrounded by hemorrhagic zones. The gross appearance of the myocardium in these instances does not indicate the type of changes that may be encountered upon microscopic examination. In studying a series of hearts by means of *multiple sections cut from many blocks*, it becomes obvious that there is practically no instance of acute endocarditis lenta which does not show one or more of the various changes which will be discussed presently. Table IX-11 is offered to show the pertinent changes encountered in the myocardium in 35 instances of endocarditis lenta (Saphir, 1935). Petechial hemorrhages were found six times microscopically, were very recent and were in no way related to embolic phenomena. *Circumscribed acute inflammatory changes with foci of necrosis and abscesses* were found 15 times. Accumulations of polymorphonuclear leukocytes were usually present in perivascular areas and often extended into the interstitial tissue between the heart muscle fibers. Small foci of necrosis in individual muscle fibers were often noted. The necrotic centers were infiltrated and surrounded by many polymorphonuclear leukocytes and here and there clumps of bacteria were present in the center of the necrosis. Outspoken abscesses were usually located just beneath the pericardium and also beneath the endocardium of the left ventricle. These are more common in acute bacterial endocarditis than in endocarditis lenta. *Acute myocarditis* was encountered 15 times among the 35 instances. This myocarditis was diffuse and consisted of infiltrations mainly of polymorphonuclear leukocytes.

TABLE IX-11

Summary of Microscopic Myocardial Changes Found in 35 Cases of Endocarditis Lenta (Saphir, 1935)

Type of Lesion	*Number of Cases*
Petechial hemorrhages	6
Acute myocarditis	15
Foci of necrosis and abscesses	15
Minute infarcts	
Recent	2
Organized	28
Healed	13
Emboli	18
Perivascular, subacute and chronic inflammation	11
Aschoff bodies	14
Perivascular fibrosis	15

Clawson (1928) found associated myocarditis in 24 per cent of his cases of endocarditis lenta and in 24.5 per cent of his cases of acute bacterial endocarditis. Yet he emphasized that while myocarditis is practically always associated with rheumatic endocarditis, it seldom occurs in the bacterial form. *Perivascular infiltrations* were encountered in 11 hearts, the predominating type of cell being the lymphocyte. Only occasionally a few plasma cells and endothelial leukocytes were also found. These infiltrations were well confined to the perivascular areas and did not extend into the adjacent parenchyma. Multinucleated cells or other cells resembling those seen in Aschoff bodies were not observed in these fields, and the cellular elements



Figure IX-25 Organizing embolus in a small coronary artery in endocarditis lenta Hematoxylin and eosin X 175

showed no particular arrangement. *Perivascular areas of fibrosis* were also often encountered, in which occasionally a few inflammatory cells were present. These areas of perivascular fibrosis were obviously old scars, but whether the original lesion was an Aschoff body or a nonspecific perivascular infiltration could not be determined In 14 instances, outspoken *Aschoff bodies* were encountered The findings of Aschoff bodies, the characteristic myocardial nodules of acute rheumatic fever, and their relation to endocarditis lenta has been discussed previously. The most commonly encountered lesions were *minute infarcts* (Figure IX-26). In endocarditis lenta these infarcts are often present in the organizing stage

Many spindle-shaped cells were found replacing heart muscle fibers. A few lymphocytes and occasional polymorphonuclear leukocytes were scattered among these cells. Often phagocytic cells were encountered, their cytoplasm filled with blood pigment. Often, too, newly formed blood vessels were present in these lesions. Recent infarcts were also occasionally encountered, infiltrated and bordered by polymorphonuclear leukocytes and a few red blood cells. Seabury (1947) emphasized that recent or old myocardial infarcts or both were found in 25 per cent of the cases in which autopsies were performed. White (1944), in stating that cardiac infarcts are very rare in endocarditis lenta, probably only referred to large infarcts recognizable grossly.



Figure IX-26 Small myocardial infarct in endocarditis lenta. Note interruption of muscle fibers by cellular scar tissue. Hematoxylin and eosin. X 175

From this description it is clear that the myocardium may show varying changes. The infarcts are easily explained by the presence of minute emboli, obviously arising from the vegetations (Figure IX-25). Larger *emboli*, blocking the mouths of the coronary arteries or the larger branches, are relatively infrequent. (In only one of the 35 instances reported by Saphir [1935] could an embolus be demonstrated in a larger branch of the coronary artery.) Emboli in the small intra-myocardial branches (Figure IX-25) obviously would be more commonly reported if they were looked for. Minute foci of polymorphonuclear leukocytic infiltrations and minute abscesses are probably the result of the lodging of bacteria in the smallest branches of the coronary arteries.

"Bracht-Wächter Bodies." Throughout the literature the term "Bracht-Wachter bodies" is often used, denoting circumscribed inflammatory lesions in the myocardium, characteristic of, but not specific for, endocarditis lenta. It is remarkable that this term is so often applied, even by those not concerned with the microscopic study of such instances, in spite of the fact that there is no clear-cut entity which could possibly be assigned such a term.

Thus, Perry (1936) stated that Bracht-Wachter bodies are cellular foci in the myocardium consisting, in early stages, of an almost equal number of polymorphonuclear leukocytes and lymphocytes. Libman and Friedberg (1948) emphasized that they replace the muscles *and are not lesions of the interstitial tissue,* while White (1944) described them as areas of mononuclear cell infiltrations of the interstitial tissue The variation in the description of the so-called "specific lesions" of the myocardium in endocarditis lenta can easily be explained by the fact that Bracht and Wächter never described a single entity Because of the existing misconception of what a Bracht-Wachter body is, it may be of interest to review *their original study in more detail.*

Bracht and Wachter (1909) did not study hearts with endocarditis lenta Working shortly after Aschoff's discovery of the *specific nodule in the myocardium* in acute rheumatic endocarditis, they were interested only in determining if an Aschoff body could be produced *experimentally* in rabbits Blood cultures, taken from two hearts in which Aschoff bodies had been found, disclosed diplo-streptococci resembling *Str. viridans* These streptococci were injected into two rabbits. Into a third rabbit were then injected streptococci which had been obtained from the heart-blood of the original two rabbits after their death. For control experiments, Bracht and Wächter used three rabbits. Two of these *were given intravenous injections of* streptococci obtained from a paronychia, and the third, streptococci isolated from infected tonsils Thus, Bracht and Wachter used only six rabbits for their experiments; three for the actual experiment and three as controls. In two rabbits, following the intravenous *injections of streptococci* isolated from the blood of a patient with acute rheumatic endocarditis, the myocardium disclosed small areas of necrosis, surrounded by lymphocytes and fibroblasts with an occasional giant cell; cellular infiltrations in the interstitial tissue, occasionally *involving the heart muscle fibers,* accumulations of lymphocytes and isolated plasma cells. The third rabbit was given an intravenous injection of blood obtained *from the hearts of the first two rabbits,* and was killed 16 days later; its myocardium showed scars replacing muscle fibers and some calcification In the myocardium of the three control rabbits only areas of necrosis were found, surrounded by many polymorphonuclear leukocytes. No normal rabbits were used as control animals

From this short review it should be clear that (1) Bracht and Wachter never studied the myocardium of endocarditis *lenta microscopically, and* (2) *in their* three experimental and three control rabbits no single characteristic lesion was encountered in the myocardium. It is hard to understand how *the term* "Bracht-Wachter body" has been able to persist in the literature. It would, therefore, seem wise to discard this term and instead use descriptive terms for the various lesions encountered in the myocardium.

Pericarditis. Pericarditis is rarely found *associated with endocarditis* lenta *but* is somewhat more frequent in acute bacterial endocarditis. In such instances there are usually small abscesses or infected infarcts in the myocardium close to the pericardium, and the pericarditis is fibrinopurulent in nature. A fresh fibrinous pericar*ditis may be the result of a concomitant* rheumatic infection, of uremia or of an intercurrent pneumonia, with acute pleuritis. A mycotic aneurysm may perforate into the pericardium, producing at *first* acute fibrinopurulent pericarditis and, later, hemopericardium (see page 694). *Among 50 cases of endocardial lenta,* Denman (1912) encountered 13 with pericarditis

EMBOLISM AND INFARCTION

Coronary Embolism or Obstruction. Gross embolism is relatively infrequent. However, of all emboli within the large branches of the coronary arteries or at their mouths, the most commonly encountered are those arising from a vegetation of the aortic valve Such large emboli may be the final contributing cause of unexpected death. Also, large vegetations of the aortic valve, soft enough so that they can be moved easily by the blood stream without breaking off, may suddenly impinge upon the mouth of one of the coronary arteries This is more likely to happen when there is also severe ulceration with rupture of either the right or left aortic cusp Multiple small emboli within the small intra-myocardial branches of the coronary arteries are extremely common These and the resulting minute infarcts, which have been regarded as the most characteristic single myocardial lesion, have just been discussed. Embolism and resulting infarcts are common in the spleen, kidneys and the brain. If the spleen is the seat of an infarct, it may actually rupture. Kennedy and Seed (1947) collected ten such instances from the literature, and reported one additional observation. Rupture usually occurs in a spleen that is the seat of an infected infarct or of a frank abscess. Perisplenitis, the result of an infarct, is common Although infarcts in the kidneys as well as in the spleen are more likely to be infected in acute bacterial endocarditis and bland in endocarditis lenta, it is not rare to find infected infarcts in endocarditis lenta. The incidence of infarction in the spleen, kidneys and brain in a series of 44 cases of acute bacterial endocarditis and of 87 cases of endocarditis lenta, as encountered by Buday, is given in Table IX-12

TABLE IX-12
Incidence of Infarction in Bacterial Endocarditis (Buday, 1929)

Disease	*No. of Cases*	*Spleen*	*Kidneys*	*Brain*	*In Various Organs Per Cent*
Acute bacterial endocarditis	44	7	10	not given	45
Endocarditis lenta	87	25	45	23	76

Buday (1929) found infarcts in various organs *in acute bacterial endocarditis in* 45 per cent and in endocarditis lenta in 76 per cent. Among Denman's 50 cases of endocarditis lenta, infarcts in the spleen were found 27 times and in the kidneys 17 times. Emboli are also often found within the *cerebral arteries and in the arteries of the* extremities. In Buday's series emboli were found 23 times in the intracranial arteries, as follows: internal carotid artery once, middle cerebral arteries 20 times, and basilar artery twice. Intestines and lungs are not often involved. Mycotic embolic aneurysms are not unusual, all such aneurysms being erosive in nature (see page 713). Such an aneurysm may involve any artery which may then rupture with resulting hemorrhage, the hemorrhage in some cases being fatal. Erosive aneurysms may also be the result of bacterial invasion directly from the blood stream without the intervention of an infected embolus.

Pirani (1943) stated that in endocarditis lenta the inflammatory process of the aortic, and rarely of the tricuspid and mitral valves, may extend into the subjacent myocardium of the interventricular septum, or into the membranous septum. In contrast to the occurrence of this complication in acute bacterial endocarditis, lesions of this type in endocarditis *lenta,* according to Libman (1913), almost never cause ventricular perforation. However, such an instance was described by Levy and Hull (1947). *Arteritis* alone may be caused by the circulating bacteria. In



Figure IX-27. Focal necrosis of kidney in endocarditis lenta. Hematoxylin and eosin X 325

endocarditis lenta, arteritis of minute arteries and inflammation of capillaries, as Libman and Friedberg (1948) stated, are sometimes presumed to be toxic, or possibly allergic lesions, inasmuch as bacteria may be absent

Various *cutaneous lesions,* such as the the *Osler nodes* (see page 750), are now believed to be the result of inflammation of the walls of the small vessels associated with endothelial hyperplasia and obliteration of their lumens. *Focal glomerulonephritis* (Lohlein's nephritis) or focal embolic glomerulonephritis (Figure IX-27), often referred to as "flea-bitten" kidney, is very common in endocarditis lenta Baehr (1912) reported microscopically typical healed embolic glomerular lesions in the kidneys of 34 of 57 patients with endocarditis lenta in the bacteria-free stage of the disease. Bell (1932) found diffuse glomerulitis in 65 per cent of patients with endocarditis lenta, and embolic or focal glomerulitis in 53 per cent of endocarditis lenta. He described two distinct types of embolic lesions, the fresh hyaline lesion, which is a capillary thrombus with necrosis of the capillaries resulting from the lodgement of bacteria, and the fibrous lesion which is characterized by a marked growth of the basement membrane of the capillaries. Bell found diffuse glomerulitis in acute primary bacterial endocarditis in 29 per cent and in secondary acute endocarditis in 33 per cent. Libman and Friedberg (1948), in quoting observations by Baehr, stated that focal embolic glomerulonephritis is almost specific for endocarditis lenta. They also pointed out that the glomerular lesion is usually produced by emboli but it is probable that local vascular inflammation and closure play a contributory, if not dominant, role in its production. The end result of such lesions is a characteristic wedge-shaped or pyramidal scar within the subcapsular space of the *glomerulus*

SEPTICEMIA

It is obvious that because of the underlying bacteremia or septicemia, changes which are usually found in uncomplicated septicemias are also encountered here Thus, cloudy swelling and fatty changes of the parenchymatous organs are common Splenic hyperplasia, sometimes of severe degree (weight of spleen, up to 800 Gm), are always encountered Because of the heart failure, which is not rare in endocarditis lenta, combinations of cloudy swelling, fatty degeneration or splenic hyperplasia with morphologic evidence of passive hyperemia in these organs may be met Because of the septicemia, *encephalitis* is not a rare complication As a matter of fact, in Kimmelstiel's (1928) experience encephalitis was more often encountered than larger cerebral hemorrhages or encephalomalacia due to emboli or embolic mycotic aneurysms.

Among the skin lesions, petechiae, Osler's nodes and Janeway lesions are usually mentioned. Petechiae are common. They may occur with or without whitish or yellowish white centers. In the skin they may be absent, or few or numerous. Sometimes they are seen best in the conjunctivae. They may be either the result of embo-

lism (although bacteria are usually not found in these lesions), the result of local inflammatory vascular lesions, or of a nonspecific proliferation of endothelial cells lining the capillaries. They are not pathognomonic of either acute endocarditis or of endocarditis lenta.

Osler's Nodes. Osler's nodes are observed in about 50 per cent of cases of endocarditis lenta. They are small, raised, red lesions about the size of a pea. They occur commonly on the fingertips, under the nails and on the soles of the feet, and more often on the upper than on the lower extremities. These cutaneous nodes are probably, as mentioned before, the result of local, possibly toxic or allergic inflammatory changes in the wall of the blood vessels. These culminate in a proliferation of endothelial cells with final occlusion of the lumina. Thus, the center of the node is often the seat of necrosis and is surrounded by a perivascular infiltration, mainly of polymorphonuclear leukocytes.

Janeway Lesions. Janeway (1899) gave the following description to the lesions which bear his name: "I have noted numerous small hemorrhages with slight nodular character in the palms of the hands and in the soles of the feet, when possibly the arms and legs had but a scanty crop in malignant endocarditis, whereas this has not been my experience with the processes likely to be mistaken for it." They are usually described as small, often hemorrhagic lesions, measuring 1 to 4 mm. in diameter, which may appear as macules or papules.

MYOCARDIAL FAILURE AND CAUSES OF DEATH

Myocardial Failure. Although modern treatment with penicillin is relatively recent, there are a number of cases on record of patients who ostensibly had been cured of bacterial endocarditis, but subsequently died of myocardial failure. This myocardial failure is explained by progressive healing of the inflammation of the valvular lesions with subsequent progressive disturbances in function.

Thus, Rosenblatt and Loewe (1945) believed that death in two of their patients was caused by cardiac failure incident to aortic valvular insufficiency. Also, Carnes and Tinsley (1946) concluded that their patients died in cardiac failure which was primarily the result of the extreme valvular damage. On the other hand, Hildebrand and Priest (1947) attributed the cause of death in their subjects to extensive myocardial lesions. Jones and associates (1947) also stated that cardiac damage caused by the infection is the chief cause of failure. Fiese (1947) emphasized that cardiac failure is common in endocarditis lenta. Eighty per cent of 40 untreated patients had evidence of cardiac failure at autopsy. He stated that cardiac failure, after otherwise successful treatment, depends on various factors, the most important being the previous heart reserve, the size of the heart, the patient's age, the type of cardiac lesion, and the height of the fever.

In the older literature it was usually stated that patients with rheumatic endocarditis eventually succumb to heart failure, while patients with endocarditis lenta die of the infection. Such a statement is obviously not true. If the myocardium is studied carefully by means of many microscopic sections, it is remarkable, as has been pointed out before, how many changes one encounters. In a study of 40 patients who died with endocarditis lenta before the era of modern treatment, Buchbinder and Saphir (1939) found that 18 of these, or 45 per cent, clinically revealed evidences of heart failure and, at necropsy, a marked degree of chronic passive hyperemia. The frequency of heart failure, as elicited clinically and as verified at autopsy, was 75 per cent. Since the infection is amenable to cure and since the acute and subacute valve lesions may heal, it seems evident that a patient who survives the in-

fection may gradually develop disturbances in function of the valves with resulting hypertrophy of the heart and thus subsequently succumb to heart failure This is particularly so because of the severe widespread damage to the heart muscle, which had occurred in the more acute stages It is easy to understand that the multiple small infarcts within the myocardium, which have been discussed before, produce permanent damage to the myocardium. Necrotic muscle fibers in the heart do not regenerate, but are replaced by scar tissue. On the other hand, it is conceivable that the myocarditis, particularly if it involves principally the interstitial tissue, may occasionally subside without permanently damaging the heart Modern treatment is designed to combat the infection, but cannot possibly have any effect upon the established infarcts, since necrosis of muscle fibers and subsequent organization and scar formation are irreversible processes Thus, patients with endocarditis lenta, despite treatment, may still have multiple small infarcts in their myocardium Since these infarcts are usually small, they may not present clinical evidence of myocardial damage Likewise, an infection that consists principally of an interstitial acute myocarditis may remain clinically silent However, if a patient with such a myocardial lesion should subsequently develop any disease, even if it be trivial, which produces an additional strain on the heart, and particularly if he should develop myocarditis or recurrence of the endocarditis with myocardial damage or coronary sclerosis, his myocardium may gradually fail.

Cause of Death in Acute Bacterial Endocarditis and Endocarditis Lenta. Patients with acute endocarditis and endocarditis lenta may die as the result of severe *septicemia.* They may succumb as the result of *embolic phenomena,* particularly of emboli in the cerebral arteries with resulting encephalomalacia and cerebral hemorrhage. They may develop large coronary emboli. *Mycotic aneurysms* may develop and death may result from a rupture of the involved blood vessel. Complicating *nephritis* may cause death. If such a nephritis is of the so-called embolic type, patients usually do not show evidence of uremia. However, if the nephritis is diffuse, death in uremia may ensue

Libman and Friedberg mentioned that death may be caused by a large vegetation acting like a ball-valve thrombus and occluding the orifice of a valve Kidd (1935) mentioned unsuspected death in bacterial endocarditis as the result of myocardial aneurysm of the conduction system. Unexpected death was reported by Munck (1946) in 18 patients with valvular disease, one patient had an acute bacterial endocarditis and two patients, endocarditis lenta Moritz and Zamcheck (1946) also reported instances of unexpected death

Although up to the present time little attention has been paid to morphologic and clinical evidence of myocardial damage, from the foregoing it must be perfectly clear that a number of patients succumb from *myocardial failure* resulting from the following three conditions: (1) multiple infarcts of the heart, (2) acute myocarditis and (3) progressive valvular impairment

BACTERIAL ENDOCARDITIS (ACUTE AND SUBACUTE) SUPERIMPOSED ON PRE-EXISTING VALVULAR DEFORMITIES

As has been stated before, acute bacterial endocarditis may be engrafted upon valves which are the seat of pre-existing deformity. Such deformity may be the result of an old endocarditis (Figure IX-28), of a congenital anomaly or, in the case of the aortic valve, of syphilis.

Bacterial Endocarditis Superimposed on Old Endocarditis. Such an old endocarditis is the result of a rheumatic endocar-

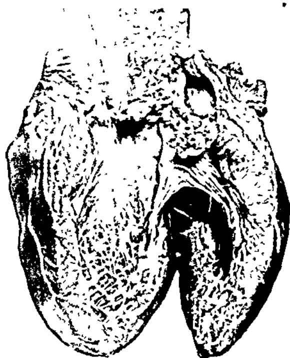


Figure IX-28 Endocarditis lenta of aortic valve, superimposed on old endocarditis both of rheumatic and syphilitic types Note syphilitic aortitis, extension of bacterial vegetations to aorta, and formation of mycotic aneurysm involving a sinus of the aortic valve (WCGH, 40 A 412)

ditis, or of a nonspecific endocarditis The old inflammation might have produced either an insufficiency of the valve or a stenosis of its orifice It has been stated repeatedly that in the presence of severe stenosis of its orifice, the mitral valve is not subject to subsequent bacterial endocarditis. However, more recent reports indicate that such valves may also be involved in acute bacterial endocarditis (see page 730) Often so-called bicuspid aortic valves, usually the result of an old endocarditis, and calcareous aortic valves, may be the seat of bacterial endocarditis Reference to the coincidental occurrence of recent and old endocarditis has been made previously.

Koletsky's (1943) report may be mentioned here. Among 50 hearts with bicuspid aortic valves, he found superimposed bacterial endocarditis in eight hearts. In four the bacterial disease was acute and in 4, subacute. A careful histologic analysis disclosed that 7 of the bicuspid aortic valves showed this deformity as a result of acquired lesions, and only one was of congenital origin. He emphasized also, that every one of these hearts showed definite stigmata of rheumatic fever.

Bacterial Endocarditis Superimposed on Congenital Heart Disease. Abbott (1926) emphasized that acute and subacute bacterial endocarditis were serious complications of cardiac anomalies. Of 555 hearts with congenital anomalies 98, or 17.6 per cent, presented an endocarditis Of these, 40 per cent were defects of the base of the interventricular septum. Brown (1939) pointed out that the risk of infective endocarditis is definitely greatest in the so-called cyanotic group of patients. He stated that the greatest frequency of infective endocarditis is found associated with patent ductus arteriosus and bicuspid aortic valve. The mode of infection is not embolic, but it seems that damage is done at points of strain and degeneration, and eventually sclerotic changes occur As Brown emphasized, these afford a nidus on which organisms circulating in the blood stream may settle and multiply It is true that vegetations do not necessarily develop just at the site of the anomalies but rather at the site of the intracardiac trauma (see page 728). This is particularly borne out in defects of the membranous portion of the interventricular septum, in which condition the vegetations are located on the septal leaflet of the tricuspid valve, since this leaflet is exposed to trauma by the blood stream flowing from the left to the right ventricle. Furlong (1944) classified the cardiac anomalies, according to the frequency in which they are involved in bacterial endocarditis, as (1) bicuspid aortic valves, (2) patent ductus arteriosus, and (3) interventricular septal defects. In regard to the associated findings of acute bacterial endocarditis and bicuspid aortic valve, it

must be remembered that a number of reported so-called congenital bicuspid aortic valves are not "congenital" but are acquired, *i.e.*, of inflammatory origin (Koletsky, 1943).

Gelfman and Levine (1942) studied material from a total of 34,023 autopsies. Among these autopsies, there were 453 instances of congenital heart disease involving persons of all ages, 181 of whom were over two years old. Bacterial endocarditis was superimposed on the congenital defect 35 times (6.6 per cent) in the whole group and 30 times (16.6 per cent) in the group of subjects whose ages were over two years. Twenty-five of the 181 hearts with congenital defects were further complicated by rheumatic infection. Table IX-13 is taken from Gelfman and Levine's article, to show the type of congenital anomaly involved by endocarditis

TABLE IX-13

Frequency of Bacterial Endocarditis in Various Congenital Anomalies,* in Patients Under and Over Two Years of Age (Gelfman and Levine, 1942)

Type of Defect	*Total Number of Patients, All Ages*	*Number of Instances of Bacterial Endocarditis*	*Percentage*	*Number of Patients over Two Years Old*	*Number of Instances of Bacterial Endocarditis*	*Percentage*
Interatrial septal defects	179	0	0	45	0	0
Interventricular septal defects	164	17	10.4	31	13	41.9
Patent ductus arteriosus	134	4	3.0	14	4	28.6
Congenital bicuspid aortic valve	63	11	17.4	52	11	21.2
Congenital pulmonic stenosis	43	8	18.6	17	5	29.4
Coarctation of aorta	33	1	3.0	10	1	10.0
Congenital bicuspid pulmonic valve	21	0	0	9	0	0
Congenital pulmonary atresia	15	0	0	2	0	0
Cor triloculare biatriatum	13	1	7.7	2	1	50.0
Congenital aortic stenosis	11	0	0	3	0	0
Congenital tricuspid stenosis	9	0	0	1	0	0
Congenital mitral stenosis	7	0	0	3	0	0
Congenital subaortic stenosis	2	1	50.0	2	1	50.0
Maladie de Roger, uncomplicated	44	10	22.7	14	8	57.1
Tetralogy of Fallot	16	2	12.5	7	2	28.6

* No case was listed if the single defect was either (1) a patent foramen ovale in a patient under one year of age unless it was 1 cm. or more in diameter, and completely or partially undefended to allow true admixture of venous and arterial blood, (2) a patent ductus arteriosus before the first postnatal month, unless the patency was abnormally wide, (3) an anomaly of the coronary arteries, the aorta or its branches, the pulmonary arteries, or the great veins, or (4) fenestration of the semilunar cusps

Incidentally, it may be mentioned that among Abbott's (1927-28) 200 recorded cases of *coarctation of the aorta* there were 14 with mycotic arteritis and mycotic aneurysms. In Gelfman and Levine's series no instance of acute endocarditis was found on interatrial septal defects. M. E. Abbott stated (in a communication to O. A. Abbott, 1941) that she had encountered, among 850 congenital intracardiac defects, only one instance of endocarditis lenta superimposed on a lower atrial defect. Saphir (1933) found a recent verrucous (rheumatic) endocarditis at the margin of the foramen ovale on its right atrial surface. There was also present an acute verrucous endocarditis superimposed on an old endocarditis of the mitral valve. Geiger and Anderson (1947) reported an instance of an interatrial septal defect and mitral stenosis, complicated by bacterial endocarditis, and referred to two other cases in the literature. It may be of interest to mention here an instance of a postoperative acute bacterial endocarditis (gram-positive diplococci) superimposed on a congenital interatrial septal defect in a dog (O. A. Abbott, 1941). More and more instan

are appearing in the literature of cures of acute and subacute bacterial endocarditis (endarteritis) in which the bacterial lesion was superimposed on a patent ductus arteriosus This cure is accomplished by surgical ligation of the ductus (Vesell and Kross, 1946, R. F. Ziegler, 1946). The difficulties involved in deciding whether or not to operate concern the medical skill, not only in diagnosing the condition, but also in ruling out the simultaneous presence of acute endocarditis of one of the valves. There are a number of instances on record in which the acute endocarditis or endarteritis had involved not only the region of the congenital anomaly, but also one or more valves (Furlong, 1944; Antenucci and Eckhardt, 1942, and others)

Bacterial Endocarditis Superimposed on Syphilitic Valvular Lesions. Libman in 1917 discussed the infrequency with which endocarditis lenta attacks valves previously damaged by syphilis. Rosenberg (1940, consult for literature) in a critical analysis, stated that up to 1940 there were reported only 10 proven instances of bacterial endocarditis superimposed on syphilitic aortic valvular disease.

Three of these 10 instances were of the acute type and seven of the lenta variety Among 24 proven instances of endocarditis lenta, Rosenberg encountered five in which this disease was engrafted upon a syphilitic valvular deformity. He also reported two instances in which acute bacterial endocarditis was superimposed upon a syphilitic aortic valve. He stated that with greater interest directed to the clinical and anatomic recognition of bacterial endocarditis superimposed on syphilitic valvular deformities, it is likely that the co-existence of these lesions may be observed more frequently than heretofore. It may be noted that Rosenberg did not make a clear-cut distinction between acute endocarditis and endocarditis lenta in his cases. Wright and Zeek, also in 1940, reported 5 cases of bacterial endocarditis superimposed on syphilitic valvular disease. They definitely ruled out a congenital anomaly or rheumatic type of valvulitis as the primary disease. They also stated that they had encountered seven additional instances of acute bacterial endocarditis associated with syphilitic aortitis but without syphilitic involvement of the aortic valve. It is of interest to mention here Forster's (1939) report of an instance of *Salmonella suipestifer* endocarditis superimposed upon a gumma of the myocardial wall. There was also a syphilitic aortitis, but the endocarditis had not involved the aortic valve. Koletsky's (1942) observation of rheumatic stigmata in four hearts with combined syphilitic heart disease and acute bacterial endocarditis has been discussed previously.

NONBACTERIAL (INDETERMINATE) ENDOCARDITIS

Gross and Friedberg (1936) separated a group of endocarditides which they considered to be of nonbacterial origin. At least up to the present time, neither a bacterium nor any other infectious agent has been demonstrated to cause "nonbacterial thrombotic endocarditis" and "atypical verrucous endocarditis," the so-called Libman-Sacks endocarditis.

Nonbacterial Thrombotic Endocarditis

Associated Condition. Nonbacterial thrombotic endocarditis has been known under the terms marantic endocarditis, terminal endocarditis, endocarditis simplex, and endocarditis minima. Gross and Friedberg (1936) emphasized that the various types of nonbacterial thrombotic

endocarditis cannot be distinguished by the histologic appearance of the lesion For this reason they classified 47 cases of nonbacterial thrombotic endocarditis according to the association of the latter with some significant clinical or clinicopathologic condition Thirty-two of their 47 cases were instances of cachectic and infectious diseases associated with chronically deformed valves, usually of rheumatic origin. Allen and Sirota (1944) reviewed the morphogenesis and significance of nonbacterial thrombotic endocarditis and termed this condition "degenerative verrucal endocardiosis" They studied material in 50 such instances The cause of death and the age at death in these 50 cases are given in Table IX-14.

TABLE IX-14

Cause of Death and Age at Death in 50 Unselected Cases of Active "Terminal Endocarditis" (Allen and Sirota, 1944)

	Number of Cases
A *Cause of Death*	
Malignant neoplasm	14
Congestive heart failure	10
Major operation	7
Pneumonia	4
Acute or subacute glomerulonephritis	2
Pulmonary embolus	2
Acute suppurative pyelonephritis	2
Congenital polyposis of gastrointestinal tract	2
Ulcerative colitis	2
Blood dyscrasia	2
Coronary occlusion	1
Periarteritis nodosa	1
Congenital heart disease	1
B *Age at Death*	
1-10	1
11-20	7
21-30	2
31-40	5
41-50	8
51-60	11
Above 60 years	16

Gross Features. The most striking and characteristic macroscopic feature is the presence of vegetations which are frequently somewhat larger than those associated with rheumatic endocarditis. The vegetations do not involve the mural endocardium or the pockets of the valves as do those in atypical verrucous endocarditis. The most common type of verrucous lesion is the so-called *pyramidal ridge* This lesion consists of narrow discontinuous bands of yellowish confluent deposits, superimposed on and firmly attached to a ridge-like thickening of the line of closure of a generally thickened valve Frequently, irregular clusters of discrete or confluent, pinhead-sized yellow verrucae are superimposed on the ridge-like thickening, giving a coronal effect. Also slightly larger, conglomerate lesions, pea-sized or even larger, are found The tendency to involve the commissures of the mitral valve or of the aortic or pulmonic valves and, only rarely, the noduli arantii of the aortic valve, is emphasized Usually the mitral valve is involved In Gross and Friedberg's series the mitral valve was involved in all cases but one, the aortic valve, 11 times, the tricuspid, 5 times and the pulmonic, twice In Moore's (1946) series, the aortic valve was the seat of the lesion 23 times, the mitral valve, 98, the pulmonic, 4, and the tricuspid, 11 times Often, previous valvular deformities were present which were usually interpreted as old rheumatic endocarditis

Microscopic Features. Microscopically, *the vegetations consist of agglutinated* blood platelet thrombi (Figure IX-29), often with early evidence of organization Along the edges of the vegetation a lining endothelium is usually recognized. Gross and Friedberg (1936) stressed, as the most remarkable feature, the paucity or absence of inflammatory cells. Only at the base of the verrucae is there usually a slight cellular proliferation with rare capillaries Polymorphonuclear leukocytes are not present and rarely are lymphocytes or plasma cells encountered. Neither the atrial nor the ventricular endocardium is involved Allen and Sirota (1944) believed that the valvular lesions are characteristically hillocks of degenerated,

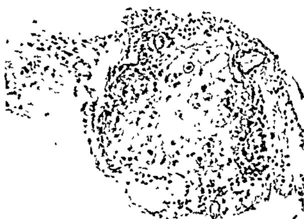


Figure IX-29 Nonbacterial thrombotic endocarditis Note presence of fibrin with few polymorphonuclear leukocytes and lymphocytes Hematoxylin and eosin X 250

valvular collagen, occasionally with an admixture of varied amounts of serum, fibrin, platelets and red blood cells, seemingly derived from permeable or eroded blood vessels of the valves

Interpretation. It is interesting that Allen and Sirota did not regard these lesions as thrombi, but believed them to be primarily degenerative and not inflammatory in nature, and hence, avoided use of the affix "itis." Also, they did not believe that these lesions are necessarily terminal. In fact, they stated that excrescences of Lambl (see under Tumors) are examples of such healed lesions They also suggested that these lesions appear to be an attractive medium for ensnaring and propagating bacteria present in the general circulation, and thus constitute an important morphologic basis for the development of bacterial endocarditis Nonbacterial thrombotic endocarditis is often reported as an incidental postmortem finding in many diseases and is obviously without appreciable clinical significance. While it does seem improbable that the verrucae themselves are of rheumatic origin, this possibility should be borne in mind. It is also possible that in some of these instances the endocarditis might have been caused by some toxic agent. Friedberg and Gross (1936) particularly emphasized the occurrence of nonbacterial thrombotic endocarditis associated with acute thrombocytopenic purpura.

The outstanding clinical findings in these patients were fever, purpura, epistaxis, bleeding of the gums, severe anemia, low blood platelet count, retarded clot retraction, a prolonged bleeding time and a rapid downward course. In each instance the disease was considered clinically to be a general infection, notwithstanding blood cultures that remained sterile. At autopsy there was enlargement of the spleen in all three of their reported cases. In two cases, there was organizing pericarditis and in the third case, there were widespread vascular lesions. It is interesting to mention in this connection that Singer, Bornstein and Wile (1947), who reviewed 12 instances of thrombotic thrombocytopenic purpura, found endocarditis associated with this condition twice.

Atypical Verrucous Endocarditis (Libman-Sacks)

Libman and Sacks in 1924 described a valvular and mural endocarditis which they termed atypical verrucous endocarditis. There were peculiar valvular and mural lesions which differed in morphology and localization from those encountered in acute bacterial endocarditis, endocarditis lenta and rheumatic endocarditis. These vegetations were free from demonstrable micro-organisms and attempts to grow bacteria from the blood proved unsuccessful. Because of the unusual character of the endocardial lesion and the presence of the verrucae the cases were designated "atypical verrucous endocarditis." Among their four cases the tricuspid and mitral valves were involved four times,

the pulmonic and aortic each twice The mural endocardium of the right atrium was involved twice, that of the right ventricle once, of the left atrium once, and of the left ventricle four times. The vegetations on the mitral valve were situated for the most part on the line of closure but extended generally below and above the latter and *also involved the free margins* The individual verrucae measured from 1 to 4 mm in diameter and had, in places, a rather broad attachment to the valve In each case the inflammatory process had spread from the ventricular aspect of the posterior leaflet of the mitral valve and the line of attachment of the latter, downward along the mural endocardium of the posterior wall of the left ventricle The lesions on the tricuspid valve were smaller than those affecting the mitral valve. Isolated areas of mural endocarditis were found quite commonly. Microscopically, the vegetations were capped by blood platelet thrombi, showing various degrees of hyaline changes, and in places the vegetations were covered by endothelium Within the deeper layers there were focal or diffuse cellular infiltrations, chiefly of round cells in three of the cases, and predominantly of polymorphonuclear leukocytes in the remaining one. Scattered among the inflammatory foci were numerous small hemorrhages. The valves in several instances showed diffuse fibrous thickening similar to that resulting from previous attacks of endocarditis It is needless to emphasize that in the myocardium there were neither Aschoff bodies nor any lesions similar to those encountered in either acute bacterial endocarditis or endocarditis lenta.

L. Gross (1940) reported the results of a study of 27 hearts showing nonrheumatic verrucous endocarditis, 23 of which were from patients with disseminated acute lupus erythematosus The valves of all of these hearts were studied whether or not they showed endocardial lesions grossly. On microscopic examination he found lesions in the heart in all of the 23 cases These were present particularly in the valve rings, valve leaflets, valve pockets, mural endocardium and pericardium Among these 23 hearts, lesions were observed in the mitral ring 11 times, in the tricuspid, 12, in the pulmonic, 8; and in the *aortic ring, 4 times The gross and microscopic* appearances of the lesions were similar to those described by Libman and Sacks Gross emphasized that the verrucae occurred frequently, were generally widespread, and were often present in the pockets of attachment of the chordae tendineae to the valve, along the chordae themselves, and on the chordal attachments to the papillary muscles ("pocket lesion") No gross ulcerations or perforations of the valves were found Microscopically, the earliest lesions consisted of cellular proliferations and degenerative changes on the surface of the valve The proliferating cells sometimes appeared to be endothelial cells, but more often they were *fibroblasts or large mononuclear cells.*

Humphreys (1948), also, stated that the endocardial lesions sometimes were difficult to detect In four hearts which she studied, the lesions had become almost completely organized She stated that they may be far from obvious, if they are flat and spread on the valvular surfaces or if they are hidden beneath the cusps or in the deeper regions between the muscular trabeculae.

Other Lesions. Libman and Sacks found, in three of their four cases, an organizing fibrinous *pericarditis.* They also reported the presence in two patients of diffuse *glomerulonephritis* which was acute in one and subacute in the other. Baehr and associates (1935) described striking vascular lesions in the kidneys and other organs Klemperer and associates (1941) particularly stressed the so-called "wire-loop" changes in the glomeruli of the kid-



Figure IX-31 Syphilitic aortitis with severe superimposed atherosclerosis Syphilitic aortic insufficiency. Note dilatation of ascending aorta and of cusps at commissures (WCGH, 45 A 351)

variably is the seat of the characteristic syphilitic lesions, with varying numbers of reddish depressed scars, wrinkles or grooves, combined with varying degrees of intimal fibrosis, foci of hyalinization and calcification (Figure IX-31). Often, too, the root of the aorta or certain regions of the ascending aorta show aneurysmal dilatations. The mouth of one or both coronary arteries is often narrowed. Sometimes the syphilitic process is observed only in the proximal segment of the ascending aorta.

Microscopic Changes. Saphir and Scott (1927) studied an apparently very early case of syphilitic aortitis, with involvement of the aortic valve. In this early instance, only widening and no hyalinization of the commissures was encountered. From a histologic study of this case and of 70 more advanced cases, they concluded that very early adhesions occur between the intima of the sinus of Valsalva and the corresponding



Figure IX-32. Syphilitic aortitis with scarring and granulomatous reaction. Hematoxylin and eosin (WCGH, 46 A 437.)



Figure IX-33 Syphilitic aortitis with stellate granuloma Note destruction of muscular and elastic fibers with scarring Van Gieson and orcein (WCGH, 36 A 394)

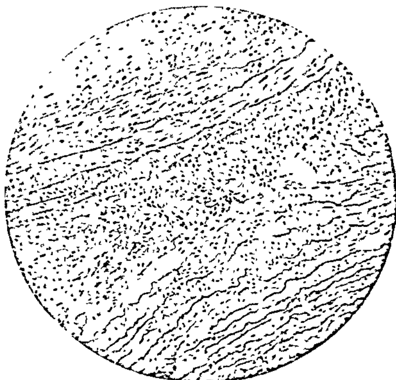


Figure IX-34 Syphilitic aortitis. Note scars in media and interruption of continuity of elastic lamellae. (WCGH, 32 A 115)



Figure IX-35 Lateral view of patient six weeks prior to death from external rupture of aortic aneurysm (WCGH, 47 A 178)

lateral and proximal portions of the aortic cusps, and that these adhesions cause the separation of the commissures. Histologically, the intima of the sinus of Valsalva and the corresponding lateral portions of the cusps first showed degenerative and later inflammatory changes. Coincident with the inflammation (Figures IX-32 and IX-33), a number of blood vessels were found which extended from the adventitia through the intima to the involved commissures and lateral portions of the cusps. Newly formed vessels also extended from the base of the cusps to their lateral and proximal borders. Fibroblasts, endothelial leukocytes and lymphocytes were the predominating types of cells. In later instances hyalinization of the intima in the region of the commissures was often encountered. Histologic examination of the more central portions of the cusps, which grossly disclosed thickening and rolling, showed only fibrosis and hyalinization, with very few cellular elements and no newly formed blood vessels. Saphir and Scott believed

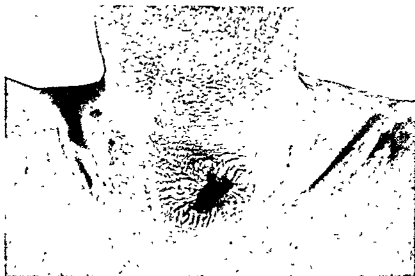


Figure IX-36 Ventral view of patient at necropsy, following external rupture of aortic aneurysm (WCGH, 47 A 178)



Figure IX-37. Ventral view of heart and aorta showing aneurysm of transverse portion of arch (WCGH, 47 A 178)

that these areas of thickening in the center of the cusps were caused by the continuous mechanical pressure of the regurgitating blood, after the *insufficiency* of the valve had been established. The centrally located margins of the cusps in early cases were neither thickened nor rolled.

Pathogenesis. If it is true that widening of the commissures is primarily the result of adhesions between the lateral portions of the aortic cusps and the adjacent aortic intima of the sinus of Valsalva, one could expect that the process sometimes would advance to the more central portions of the cusp and corresponding intima of the sinus of Valsalva; that the adhesions would not necessarily be confined to the commissures but might extend toward the center of one or both adjacent cusps, with consequent adhesions between the cusps and the aortic intima of the corresponding sinus of Valsalva over a wide area. Such adhesions would lead to severe narrowing of the respective sinus of Valsalva, or perhaps even to obliteration of the sinus, or the transformation of the sinus into a blood-filled cavity with resulting extreme regurgitation of the valve Interestingly enough, two such instances have been encountered by Saphir and Stasney (1933) In one of these (Figure IX-38), one sinus of Valsalva was actually transformed into a blind cavity and in the other, a part of the sinus had almost completely disappeared because of widespread adhesions between the aortic intima



Figure IX-38. Extreme widening of the commissures The pointer is directed to the sinus of Valsalva corresponding to the posterior aortic cusp which is almost completely obliterated Note marked separation of the cusps at commissure between the posterior and right aortic cusps The interventricular septum presents several diastolic endocardial pockets,

and large portions of the cusp. These authors found only eight similar cases in the literature. Particularly pertinent is one *described by Rokitansky and reported by* Maresch (1931). It was labelled, as translated from Latin by Maresch, as follows: "A dilated and hypertrophic heart with the large vessels from a 50-year-old woman. At the root of the dilated and thickened aorta, the right valve, because of adhesions to the vessel, appears absent and the mouth of the coronary artery obliterated." Jason (1941), who also studied syphilitic deformity of the aortic valve in 27 hearts, did not emphasize differences of the central and lateral portions of the cusps. He concluded that all of the valve distortions appeared to have been caused by two processes: (a) a destructive inflammation of the aortic wall resulting in destruction and dislodgement of the attachments of the cusps at the commissures, and (b) a reparative fibrosis. *However, it would seem difficult* to explain the extreme involvement of the aortic valve in syphilis, as related above, on this basis. Just why there is a predilection of syphilis for the base of the aorta and the region of the commissure is difficult to explain. Saphir and Scott (1927) believed that this area of the aorta shows more vasa vasorum than any other region of the aorta. This is in agreement with Spalteholz. Syphilis is a primary disease of the vasa vasorum and, therefore, of greater significance in areas containing a large number of vasa vasorum. It appears in the vast majority of cases that syphilitic valve lesions occur only with involvement of this segment of the aorta. *Spirochetes* have been demonstrated in the aortic valve involved by syphilis. Šikl and Raska (1935) reported the lesion in two adults, in one of whom numerous spirochetes could be demonstrated by Kanzler's method. Only a few spirochetes were found in the heart of the second patient.

Gumma of Aortic Valve. Invasion of the heart valves by gummas is also described in the literature. Richter (1936) stated that there had appeared in the literature *only eight adequately described instances* of *gummatous endocarditis* of the *aortic valve*, resulting from invasion of the cusps by a syphilitic process in the root of the aorta or from a gumma of the interventricular septum. He described an instance of gummatous endocarditis of the aortic valve in which the *Treponema pallidum* was demonstrated. In this instance a congenital bicuspid aortic valve and subaortic stenosis also were present.

It should be mentioned here that there also are on record cases of combined syphilitic and rheumatic aortic valvulitis (Figure IX-28). Lisa and associates (1942) reported 9 such instances.

There are also many instances of syphilitic aortitis without separation of the commissures but with severe *dilatation or "stretching" of the root of the aorta*, including the sinus of Valsalva (Figure IX-34), with resulting insufficiency of the aortic valve. This stretching of the aortic ring is the result of the syphilitic process in the adventitia and media of the aorta itself. In such an instance the cusps may also enlarge and for some time effect adequate closure (Karsner, 1949), but eventually insufficiency of the valve ensues

Patients with syphilitic aortic insufficiency and stenosis of the mouth of one coronary artery often succumb unexpectedly. Martland (1930) found at autopsy that in 101 cases of sudden death caused by syphilis of the aorta and heart, aortic regurgitation was the predominating lesion in 36 cases, and stenosis and atresia of the coronary ostia in 15.

Histologic Changes at Mouth of Coronary Artery. Such changes have been studied by Burch and Winsor (1942). The adventitia of the coronary arteries showed an accumulation of small round cells, particularly about the vasa vasorum. *The in-*

flammation usually begins (Moritz, 1931) about the vasa vasorum in the adventitia of the vessels and extends along the smaller vessels into the media and intima. The media becomes infiltrated with lymphocytes and small round cells, which replace the healthy muscle and elastic tissue. The intima is greatly thickened as a result of the formation of succulent vascular inflammatory plaques, which occlude the ostia of the coronary arteries in the regions where they pass through the aortic wall. Such exudative, edematous lesions may encircle the aortic root, forming the so-called "girdle of Venus" (Leary, 1940) When the coronary ostia are involved, usually only the first 3 mm of the artery are affected, and beyond this point the vessel is wider and remains patent throughout its entire length.

Syphilis of Mitral Valve. Syphilis of the mitral valve has been a *much disputed* subject in the older literature The fact that syphilitic aortic insufficiency may be present in a patient who also happened to have an old inflammatory lesion of the mitral valve with or without functional disturbances, does not at all imply that the mitral lesion is also syphilitic in nature. On the contrary, it is probable that such a mitral lesion is invariably coincidental, the result of a nonspecific inflammation or of a rheumatic infection. Blackman (1935) stated that extensive syphilitic lesions of the mitral valve have rarely been described. In the two hearts reported by Blackman, syphilitic changes were continuous with syphilitic lesions at the root of the aorta and the aortic valves, and were present in the membranous septum of the heart and the aortic leaf of the mitral valve. Grossly, the lesions consisted of a diffuse leathery thickening of these areas Microscopically, *gummatous necrosis or dense* vascular scars with perivascular round cell infiltrations were found. It is interesting that only the aortic leaflet of the mitral valve was involved. It must be emphasized that there are only two extremely rare possibilities for involvement of the mitral valve in syphilis Either gummas may be present in the mitral valve or the adjacent myocardium, with secondary extension into a leaflet, or the syphilitic process may extend from the base of the aortic valve downward to the aortic leaflet of the mitral valve. However, such instances are extremely rare, so rare in fact that it may well be stated that syphilis practically *never involves the mitral valve*

Syphilis of Pulmonary and Tricuspid Valves. Syphilis may, extremely rarely, involve the pulmonary valve Such instances, of course, are always associated with syphilitic pulmonary arteritis.

Plenge's (1929) second case showed an involvement of the pulmonary valve. Another clear-cut instance was reported by De Navasquez (1942) There was a syphilitic pulmonary arteritis and the pulmonary valves disclosed typical widening of the commissures. Gummatous involvement of the pulmonary and tricuspid valves, in addition to the mitral valve, have also been reported (Richter, 1936).

CONGENITAL (FETAL) ENDOCARDITIS

Valvular Endocarditis. In the older literature there are a number of reports of so-called fetal endocarditis (Figure IX-39). Ribbert (1924) *maintained that such an* endocarditis could occur during the last month of gestation and only after the valves had been well formed. He thought that the occurrence of such a fetal endocarditis was rare Though fetal endocarditis, *as characterized by the presence* of a verrucous vegetative inflammation, has never been observed, he asserted



Figure IX-39 So-called *congenital endocarditis* of pulmonic valve This is not a true endocarditis, but the valves still show material constituting the original endocardial cushion

that it might be recognized in an old stage by the presence of fibrous thickening in the valves. He emphasized that there are great difficulties in interpreting older valvular lesions *in infants, and often* it cannot be decided whether they are the result of an old endocarditis or of a congenital malformation. Ribbert pointed to the relatively frequent combination of so-called endocarditis and malformation of the heart. He stated that either during the *fetal period or shortly after delivery* the inflammatory processes were probably superimposed upon a congenital malformed valve. Cappelli (1933) noted microscopic changes in many fetal hearts which *he interpreted as* valvular *endocarditis.* However, P. Gross (1941) thought that the significance of these observations appears rather dubious in view of the frequency (75 8 per cent of 67 unselected cases) with which these lesions were found. Gross stated that a careful analysis of the cases reported in the literature reveals that *myocardial scars or myocardial* fibrosis, prerequisites for the diagnosis of fetal endocarditis, was noted in 78 per cent of the cases listed as fetal endocarditis. On the other hand, these lesions also have been *found in 38 per cent of cases* considered to be instances of non-inflammatory changes. A number of writers noted that the papillary muscles showed the most marked lesions in "fetal cardiac inflammations." These observations may be matched by reports of similar alterations which are considered to be non-inflammatory. *Valvular excrescences, often termed* vegetations, were noted in 11 of 53 cases designated as fetal endocarditis, and in four of 23 cases in which this diagnosis was made in the material collected by Gross. *It is interesting that in the few instances* in which these valves were examined histologically, these excrescences were described as composed of embryonic connective tissue. In not a single instance was there unequivocal evidence of inflammation. Thus, Gross concluded that the occurrence of fetal endocarditis has never been *established. The macroscopic* and microscopic abnormalities, considered criteria of fetal endocarditis, have been observed also in the presence of congenital cardiac defects and, after study, have been diag*nosed as non-inflammatory* lesions. The valvular changes seen in these cases are *better explained on the basis of a* developmental defect, since they show no inflammatory residua. From an examination of a large number of hearts with various congenital anomalies, and deformities of *valves, we must also agree* with Gross' findings. The reddish gelatinous material simulating broad-based, smooth vegetations which is occasionally encountered in infants' hearts, constitutes the remains of a myxomatous mesenchymal tissue and

cannot be regarded as organizing vegetations. True residua of inflammation are never present.

McDonald (1950) described valvular thrombotic vegetations in a newborn These were interpreted as bland thrombi which had formed on surface irregularities in the development of valvular hematomas, or as a result of hypothetical rupture of blood cysts found on the cardiac valves of the newborn The possibility was also suggested that this lesion may be identical with the exudative type of verruca found in degenerative verrucal endocardiosis described by Allen and Sirota (see page 755).

Whitish pink, apparently edematous, nodules in the region of the attachment of the chordae tendineae to the atrioventricular valves are occasionally found in children and are referred to as *noduli albini* They consist of myxomatous material and may be considered as remnants of portions of the original endocardial cushion They are of no clinical significance.

CONGENITAL PARIETAL ENDOCARDIAL FIBROSIS (SCLEROSIS)

Gross also devoted considerable attention to opaque, glistening, white or yellowish white thickenings of the parietal endocardium in infants' hearts, with or without valvular deformity These lesions had been classified as fetal inflammation by some investigators and as developmental anomalies by others. He emphasized that diffuse endocardial fibrosis is devoid of inflammatory residua and is best explained as simple hyperplasia of the endocardial fibroelastic tissue. The decision as to whether this is secondary to circulatory changes or is a primary developmental defect is easier to make in those cases in which such endocardial sclerosis is found unassociated with valvular defects Such cases are to be found in the literature (see Gross). Thus, Gross classified these parietal endocardial changes, not as an inflammatory lesion, but as a developmental defect. Sano and Anderson (1942), in discussing endocardial fibrosis in infants, spoke of "endocardial hyperplasia" which they encountered in 3 instances They were impressed with the large amount of elastic or fibroelastic tissue within the whitish endocardium, as demonstrated by special stains.

Weinberg and Himelfarb (1943) reported on two infant siblings, the heart of one having a diffuse grayish white thickened endocardium confined to the left ventricle, while the heart of the other had additional tiny foci of endocardial thickenings in the right atrium and ventricle The first infant also disclosed a severely narrowed ascending aorta proximal to the obliterated ductus arteriosus. Microscopically, the thickening of the endocardium was demonstrated to have been produced by an increase mainly of elastic fibers and partly of collagenous fibers They applied the term "fibroelastosis" to this lesion. The fact that the fibroelastosis occurred in siblings and that there was no history of any infection in the mother during either period of pregnancy militates against the concept of fetal endocarditis as an intra-uterine infection, and supports the suspicion of an inherent developmental defect.

Weinberg and Himelfarb thought that the endocardial fibroelastosis can explain the failure of the heart With the development of such a thick fibroelastic layer one can postulate, they assumed, some interference with the emptying of the arterioluminal vessels into the ventricle, because of constriction of their orifices by the

elastic tissue. Thus, with the establishment of obstruction to the flow of blood, partial stasis may develop within the intramyocardial capillaries. This leads to some degree of anoxemia and eventually to myocardial damage and myocardial failure.

Cosgrove and Kaump (1946) studied endocardial sclerosis in infants and children. Almost all of their subjects showed evidence of congenital anomalies. They particularly stressed that the microscopic appearance of the valve rings, with their myxomatous stroma and absence of lymphocytes and polymorphonuclear leukocytes, calls to mind congenital rests. Although myocardial lesions were present, they resembled infarctions rather than inflammatory lesions. This appearance, together with the relatively complete occlusion of the smaller arterial and venous channels, emphasizes the probability of the congenital nature of primary endocardial sclerosis

Craig (1949) described congenital endocardial sclerosis in 37 instances of congenital heart disease In the majority of these cases there was an associated malformation of the valves. It was noted that this lesion occurred more commonly in males than in females and was found much more often in the left ventricle than in the right ventricle. He discussed the various causes of the endocardial sclerosis and refutes all of them. It seemed most likely to him that both the valve lesions and endocardial lesions were the result of abnormalities of development rather than due to an infectious process. Also, myocardial degeneration and fibrosis were frequently present in the subendocardium. This was thought to be the result of anoxemia.

Prior and Wyatt (1950) expressed the opinion that endocardial fibroelastosis may constitute a developmental disorder of mesenchymal tissue and hence may be classified with congenital cardiac malformations. They suggested the term "endocardial dysplasia" to replace "fetal endocarditis" and "endocardial fibroelastosis," both of which have misleading connotations.

In this connection, it may also be mentioned that in certain instances of congenital anomalies of the heart, particularly in those which cause deviation in the direction of the normal flow of blood, there is often a diffuse thickening of the endocardium (Taussig and Semans, 1940). In summary, it is thus evident that the whitish endocardial plaques in newborns and infants consist of both connective tissue and elastic lamellae They probably are the result of developmental anomalies and are not caused by inflammation.

Acquired Parietal Endocardial Fibrosis (Sclerosis)

Acquired endocardial sclerosis may be more or less diffuse, involving principally the left ventricle and particularly the endocardium of the interventricular septum; or it may be spotty or circumscribed. The former variety is much rarer than the latter.

Diffuse Parietal Endocardial Fibrosis (Sclerosis). In the diffuse variety of endocardial sclerosis (Figure IX-40), on opening the left ventricle, the endocardium presents a more or less diffuse whitish or ivory white appearance and, when incised, discloses a thickness of one or two millimeters. The endocardial thickening may involve also the papillary muscles. A number of causes are postulated for diffuse endocardial sclerosis, the predominating ideas considering them to be the result of (1) primary lesions of the myocardium, (2) hypertension, (3) congenital anomalies of the origin of the coronary arteries, (4) inflammatory conditions, and (5) developmental defects involving the parietal endocardium (see page 767).

1. Endocardial thickening may be the result of *primary lesions of the myocardium*. In many instances of large old infarcts of the myocardium, the overlying



Figure IX-40. Diffuse endocardial fibrosis. Note whitish appearance and severe thickening of endocardium. The aortic valve consists of remnants of original endocardial cushions

endocardium is white and thickened. Such thickening may extend over large areas and is not necessarily confined to the region of the infarct. There are two explanations for this endocardial thickening. According to one explanation, as a result of the occurrence of infarcts, aseptic mural endocarditis develops and this undergoes healing and eventually forms whitish scar tissue. This endocarditis corresponds to the pericarditis observed in hearts with myocardial infarcts. Such a pericarditis is not necessarily circumscribed but may be diffuse. Another explanation for such an endocardial fibrosis is that it constitutes the end stage of organized mural thrombi which had been present adjacent to the infarcted area. Such endocardial thickenings, extending over larger areas, are so significant that an old infarct must be considered immediately, in such instances. There are no elastic lamellae in these lesions.

2. There are a number of cases on record of diffuse endocardial sclerosis involving particularly the endocardium of the interventricular septum. Such instances are thought to be the result of a *marked permanent increase in the systolic arterial blood pressure* (see Ribbert, 1924). However, such a cause has never been proven, though circumscribed areas of thickening, in instances of functional disturbances of the various valves, are often interpreted as being the result of either the systolic or regurgitating diastolic blood currents and pressure (see page 772). Yet, there are cases of endocardial fibrosis on record, particularly in children, without associated valvular abnormalities or changes in the coronary arteries or myocardial lesions. Since this endocardial sclerosis is usually found in hypertrophic hearts, hypertension has been suggested as its cause.

Taussig and Remsen (1935), in their report of essential hypertension of a two-year-old child, referred to the endocardial lining of the left ventricle as "smooth but slightly thickened." Also, in one of Abbott's (1928) cases of coarctation of the aorta, mention was made of an endocardium that had a thick "sugar-icing."

3. Levine (1934) reported a uniformly and diffusely thickened and opaque endocardium in a 10-month-old infant. The heart was hypertrophic. There was narrowing of the descending branch of the left coronary artery and coarctation of the aorta of the infantile type. No inflammatory reaction was seen in the heart. This and other similar instances raise the question whether the endocardial fibrosis, in these cases, constitutes a congenital anomaly *per se* or whether it is the result of the hypertension consequent to coarctation of the aorta. Endocardial thickening, usually associated with cardiac hypertrophy is almost invariably present in cases in which the *left coronary artery arises from the pulmonary artery.* References to the pertinent literature up to 1932 may be found in the communication by Bland and associates (1933).

These workers reported this condition in a male infant three months of age with a marked hypertrophy of the left ventricle. Grossly, the entire endocardium of the left ventricle was whitish and thickened.

Microscopically, the connective tissue had extended also into the adjacent myocardium The myocardium showed severe degeneration and diffuse connective tissue displacement. There was an apparent increase in the number of muscle fibers and also a separation of the muscle bundles by unusually large spaces, seemingly the result of vascular dilatation, together with a small amount of fibrosis between the bundles In later studies, particularly by Soloff (1942), many dilated blood vessels were encountered and interpreted as a persistence of embryonic sinusoids, brought about by the lack of sufficient anastomosis between the right and the left coronary arteries Bland and associates stated that the lack of adequate vascular supply to the myocardium seemed so severe as to have caused not only myocardial fibrosis, but actually aneurysms of the heart. Subsequent case reports by Soloff (1942), Proescher and Baumann (1944) and Eidlow and Mackenzie (1946) described instances with hypertrophy of the heart, fibrous replacement of the myocardium and severe thickening of the endocardium of the left ventricle.

4 *Inflammation* as the underlying cause of diffuse endocardial fibrosis was reported by Comeau (1937) In both of his cases there was evidence of severe myocardial damage In one particularly, there was a diffuse and focal lymphocytic infiltration with giant cells and granuloma-like lesions He emphasized that in a group of cases of diffuse parietal endocardial sclerosis, a compensatory protective change in the endocardium is secondary to an organic subendocardial "weakness." Such a mural endocarditis obviously is the result of an extension of a primary myocarditis to the adjacent mural (parietal) endocardium. The endocardial sclerosis is the final result of the mural endocarditis in these instances.

Loffler (1947) has described "endocarditis parietalis fibroplastica," in which there is thickening of the parietal endocardium of both ventricles, the valves themselves being normal. This entity is often accompanied by eosinophilia, particularly in its early stages. Because of the fact that occasionally streptococci were cultured from the various organs (so-called dissociated streptococci), and because in one case Lohlein's nephritis was encountered, Loffler believed this disease to be somehow related to endocarditis lenta. Egger (1944) described a similar condition under the term "endocarditis obliterans" and linked it to endarteritis obliterans (Buerger's disease). In Egger's case the associated clinical findings were severe dyspnea, cyanosis, enlargement of the liver, edema of the lower extremities, ascites and hydrothorax. The differential leukocyte count disclosed an eosinophilia of 15 per cent. The mural endocardium of both the right and left ventricles was severely thickened and covered with thrombi. The lumen of the left ventricle was narrowed to the diameter of the lumen of the ascending aorta. The valvular apparatus was intact and the coronary arteries were unchanged. Microscopic examination disclosed a subacute and chronic inflammation with predominance of lymphocytes and plasma cells in both the endocardium and adjacent myocardium Perivascular inflammatory cells were frequent and there was also granulation tissue and young connective tissue. Despite a history of rheumatic fever, Egger considered that the inflammatory disease of the myocardium and the mural endocardium should be classified as an allergic inflammation. Lennox (1948) reviewed the literature and gave data on 6 such instances. He described, in a 53-year-old woman who had eosinophilia and died of status asthmaticus, an extensive cellular infiltration of the endocardium of the left ventricle. He thought that a secondary mural thrombosis

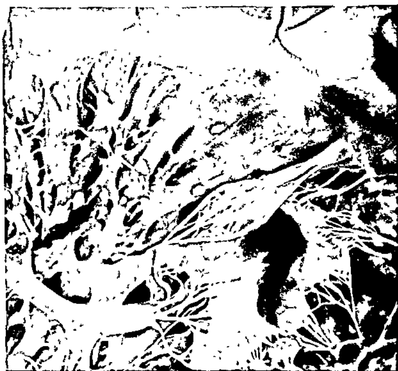


Figure IX-41 Multiple localized areas of endocardial fibrosis Old endocarditis of mitral and aortic valves.

followed by organization would exactly duplicate the end result of Loffler's endocarditis.

Circumscribed Parietal Endocardial Fibrosis (Sclerosis). Circumscribed fibrous thickenings of the endocardium, so-called circumscribed endocardial sclerosis, is common (Figure IX-41) It is usually present in the left ventricle and often involves the endocardium covering the interventricular septum, but is also occasionally found in the right ventricle and in the left atrium. It is sometimes difficult to decide whether such localized endocardial fibrosis is the result of a preceding primary *inflammation*, an underlying *infarct* (see page 768, or of *abnormal blood currents* and eddies in functional disturbances of the heart valves. Of particular interest are the latter. Areas of circumscribed endocardial fibrosis are often present in association with insufficiency of the aortic valve. In such cases the thickened plaques may be found anywhere in the left ventricle with the exception of the posterior wall and of the apical portions of the heart. Most commonly they are present on the interventricular septum, and not rarely on the endocardium of the aortic leaflet of the mitral valve and bridging over the trabeculae carneae. Because such a circumscribed endocardial fibrosis so often accompanies aortic insufficiency, it is not surprising that, as early as 1895, Zahn thought that these simple endocardial thickenings were produced by the continuous irritation of the impulse of the regurgitating blood. He also observed circumscribed endocardial sclerosis in the left atrium in instances of insufficiency of the mitral valve. However, others (Ziegler, 1908, Aschoff, 1919) emphasized that circumscribed endocardial fibrosis (sclerosis) is often primarily inflammatory in nature, representing the end stage of acute mural endocarditis. This view is supported by the frequent finding of circumscribed endocardial fibrosis in hearts which are the seat

of old inflammatory valvular conditions. Yet, it is well known that rheumatic endocarditis, which probably is the most common cause of valvular deformities, does not cause ventricular mural endocarditis. Besides, circumscribed endocardial fibrosis is often seen in instances of syphilitic aortic insufficiency while syphilitic inflammation does not involve the mural endocardium. Thus, the genesis of circumscribed endocardial fibrosis, at least in these instances, cannot be primarily inflammatory. In histologic studies of such circumscribed endocardial fibrosis, rarely will one encounter inflammatory changes (Saphir, 1930). The histologic changes will be discussed below.

ENDOCARDIAL POCKETS

In cases of insufficiency of the aortic valve, an associated and striking finding is that of endocardial pockets, imitating the form of valve cusps. They are most commonly situated on the *interventricular septum of the left ventricle* and are rereferred to in the older literature as Zahn's (1895) or Schmincke's (1908) pockets. They are often multiple with their openings directed toward the aorta. More rarely, pockets are observed just *beneath the aortic valve* with their openings directed toward the apex of the heart. In such instances there is present also stenosis of the orifice of the aortic valve or an actual or relative narrowing of the aortic conus. Much rarer are endocardial pockets in the *left atrium;* here the openings are usually directed toward the mitral valve which invariably is insufficient. Though endocardial pockets are not rare, they have received little attention. Yet there are in the field of pathology only a few anatomic structures which are so characteristic as to indicate a definite functional disturbance. The relevant literature is given by Saphir (1930). These lesions arise principally as circumscribed endocardial thickenings, before they become fully established as pockets. While it is possible that some endocardial thickenings are the result of a circumscribed primary mural endocarditis, it seems much more likely that the primary endocardial fibrosis is the result of an *abnormal regurgitating blood* column or perhaps pressure, with the formation of eddies. In instances of stenosis of the aortic orifice or of the uppermost portion of the left ventricle, just below the aortic valve (conus), it is possible that the friction of the systolic blood stream and pressure produces mechanical irritation of an area situated at the entrance into the stenosed region.



Figure IX-42. Circumscribed endocardial thickening and diastolic pocket characteristic of insufficiency of aortic valve.

Diastolic Pockets. In instances of insufficiency of the aortic valve, the continuous impact of the regurgitating diastolic column of blood exerted upon a localized area of young connective tissue may well undermine this excess of tissue and produce a pocket, its opening directed toward the aortic valve (Figure IX-42). Ingham

and Henthorne (1938) stated that, for want of a fuller explanation of the cause of these lesions, the theory of mechanical irritation of the endocardium caused by abnormal blood currents is accepted as the most logical. Krasso (1925) named such pockets "diastolic pockets." Diastolic pockets are found more often in hearts with syphilitic aortic insufficiency than in hearts with insufficiency of the aortic valve from other causes, because the insufficiency of this valve resulting from syphilis is brought about by the separation of the cusps at the commissures. Because of this, the path of the regurgitating blood columns is narrow and more rigid (Kaewel, 1928) than in those instances in which the insufficiency is the result of retraction of the cusps It seems conceivable that the narrow, regurgitating blood column in hearts with syphilitic valves is directed more or less towards one circumscribed area of endocardium, with resulting fibrosis and subsequent pocket formation. Saphir (1930) found diastolic pockets in 15 of 93 cases of clinically recognized aortic insufficiency. In some instances only one or two pockets were found, in others, actually rows of three or four, sometimes at different levels. This would indicate, perhaps, a gradual increase in the degree of insufficiency. Saphir emphasized that the presence of diastolic pockets on the interventricular septum of the left ventricle is pathognomonic of insufficiency of the aortic valve.

Systolic Pockets. Sometimes pockets are found *on the interventricular septum*, their openings directed towards the apex. Krasso (1929) called such pockets systolic pockets It seems that the continuous pressure exerted upon the entrance of a *stenosed aortic conus*, or upon the mural endocardium just below a *stenosed aortic valve* orifice, may undermine a localized area of early fibrosis and produce a systolic pocket. In Saphir's (1930) series,



Figure IX-43 Atrial pocket facing open foramen ovale, just to left of upper arrow.

systolic pockets were encountered more often in instances of relative stenosis of the aortic conus in hypertrophied and dilated hearts (The conus aorticus, often called conus arteriosus sinister, is the most cephalic portion of the left ventricle located just inferior to the aortic valve, Krasso, 1925) Saphir concluded that systolic pockets, situated on the interventricular septum, or anterolateral wall of the left ventricle, are pathognomonic of stenosis, either of the orifice of the aortic valve or of the conus aorticus. Systolic pockets are also found in the left atrium above the mitral valve, in instances of insufficiency of this valve. The opening of these pockets is directed towards the mitral valve (Figure IX-43). They are much rarer than ventricular pockets. Hellerstein (1947) concluded that prolonged regurgitation of blood and the resulting pressure are the most significant factors in the development of these endocardial pockets Saphir emphasized that these atrial pockets are pathognomonic of insufficiency of the mitral valve.

Microscopically, Ingham and Henthorne (1938) found the cusps of these pockets

or pseudovalves to be composed of the loose form of adult connective tissue peculiar to normal heart valves. The subendocardial elastic tissue was split to form lamellae on both the inner and outer surface of the pseudovalve and also provided a fine elastic meshwork for the connective tissue structure. There was no evidence of inflammatory reaction at the base of this pocket. A definite hyaline thickening of the endocardium was found close to it. They emphasized that the pseudovalve or pocket had every appearance of a normal young heart valve. Hellerstein (1947) also described reduplication of the elastic fibers *above and below the pockets and* extension of the elastic lamellae, from the endocardium into the pockets He, too, remarked on the absence of any vestiges of inflammation Saphir, however, in a few pockets demonstrated blood vessels and residua of inflammation.

Significance. Thus, it would seem that the presence of pockets materially aids in the diagnosis either of insufficiency of a valve or of stenosis of a valve orifice or aortic conus. The original young connective tissue formation is seldom primarily the *result of a mural endocarditis,* but much more often the result of a mechanical irritation Once circumscribed young connective *tissue is formed, continuous pressure* and mechanical irritation will cause a secondary excavation and the formation of a pocket or so-called pseudovalve. Depending upon the direction of the irritating blood columns and mechanical trauma, the pockets will show an opening directed either toward the valve or away from it. Wilke (1910) and also Borst (1919) stated that such pockets are manifestations of functional adaptation. Functional adaptation, however, implies that the part involved adapts itself to new functional demands (Karsner, 1949) and actually fulfills the functions demanded (Borst). *These endocardial pockets only resemble* pockets of the aortic valve. Even though they are brought about by the force of the blood stream and are often multiple, they can have no function because they are small, and hold only an insignificant amount of blood. To fulfill a function, it would be necessary that many be present, that they be large and close enough to each other to allow their cusps to touch, during diastole, as aortic cusps do. This, of course, holds only for diastolic *pockets in* aortic insufficiency. Systolic pockets cannot *possibly be interpreted as* having any function whatsoever.

SUBAORTIC STENOSIS

There is perhaps a relationship between endocardial sclerosis, systolic pockets found on the endocardium of the interventricular septum just beneath the aortic valve, and the so-called "subaortic stenosis" *of the left ventricle* (Figure IX-44). Leading reviewers (see Gruenwald, 1947) of heart malformations mention the occurrence of subaortic stenosis in the outflow tract of the left ventricle of the heart and class it as a congenital abnormality ("congenital subaortic stenosis"). While it is true that subaortic stenosis has repeatedly been found in combination with malformation of the heart, this is not the rule and did not hold for 6 such instances described by Gruenwald. In subaortic stenosis *the endo*cardium covering the aortic outflow tract, *at a varying distance below* the valve, is diffusely thickened and grayish white. The thickening is often semicircular and projects into the ventricular cavity, causing stenosis of the aortic outflow tract. Very often, and in fact in all instances reported by Gruenwald, the lower border of the thickened endocardium is *more or less*

sharply defined and partly undermined, forming one or several pockets with openings directed toward the apex (systolic pockets) Gruenwald concluded that subaortic stenosis may constitute a primary *maldevelopment and may be the result of* a fetal inflammation (see page 767) with subsequent congenital abnormality, or may have a postnatal origin. In regard to a primary maldevelopment, it must be emphasized that, so far at least, no compelling embryologic explanation of such a malformation has been given, though Keith thought it might represent a remnant of the bulbus cordis In regard to possible fetal inflammation, it must be recalled that Gross (1941) brought forward sufficient evidence to refute congenital inflammation as the cause of endocardial fibrosis.

It is remarkable that in many instances of reported subaortic stenosis there are also lesions in the aortic valve causing stenosis of its orifice, or hypertrophy and dilatation of the heart from other causes, which may lead to a relative stenosis of the aortic conus Two of Gruenwald's hearts disclosed obvious stenosis of the aortic orifice (rheumatic), another one *"slight fusion of two cusps of the aortic* valve." If there is fusion of two cusps, the circumference of the valve orifice must be narrowed and stenosis is present. Another heart disclosed "arteriosclerosis" of the aortic valve with calcific plaques, and still another was "severely hypertrophic and dilated" Thus, it is clear that many of the reported hearts with subaortic stenosis also showed lesions which, as stated above, may give rise to circumscribed endocardial fibrosis (sclerosis) with subsequent formation of systolic endocardial pockets *All of Gruenwald's 6 hearts showed, not* only subaortic stenosis, *i.e.*, annular or arched circumscribed endocardial sclerosis, but also systolic pockets. Thus, it would seem at least possible, if not probable, that subaortic stenosis is an exaggerated, circumscribed, endocardial sclerosis, caused either by mechanical trauma (Sternberg, 1930) or, rarely, by mural inflammation with secondary formation of systolic pockets. It should not be classed with congenital malformations of the heart On the other hand, it is conceivable that certain malformations, such as bicuspid aortic valve *and coarctation of the aorta* (Enzer, 1927), may provoke a functional abnormality or stenosis of the aortic conus which, in turn, causes subaortic circumscribed *endocardial fibrosis* (stenosis) with secondary formation of systolic pockets. So-called subaortic stenosis may also be complicated by what has been interpreted as endocarditis lenta or by acute bacterial endocarditis (Walsh *et al.*, 1943).



Figure IX-44 Subaortic stenosis Note fibrosis of endocardium beneath patent interventricular septum of pars membranacea, with systolic pockets

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Nonrheumatic Inflammatory Diseases of the Heart

C. Myocarditis

DIAGNOSIS OF MYOCARDITIS

In the past when myocardial fibrosis, the result of coronary artery disease, was not distinguished from primary inflammatory disease of the myocardium, "myocarditis" was diagnosed often and was an accepted cause of death on official death certificates After the morphologist had convinced the clinicians of the advisability of limiting the term "chronic myocarditis" to conditions showing evidence of true primary inflammation of the myocardium, myocarditis became a rare diagnosis. Renewed interest in the myocardium in a number of infectious diseases and careful morphologic studies of the myocardium have convinced the pathologist that true myocarditis is not a rare disease; that it may accompany most bacterial and many virus diseases; that occasionally it may appear as a special, perhaps primary disease entity; and that it may cause death. In the light of these anatomic studies it seems remarkable how rarely myocarditis is diagnosed clinically; how seldom it is even considered. The reason may be that in modern medical training functional disorders are stressed rather than the anatomic changes which produce such disorders; so that, in the case of heart disease, the emphasis is more likely to be placed on circulatory failure than on anatomically demonstrable myocardial changes.

Thomas Lewis (1934) stated that the use of the term "myocarditis" is scarcely

justified clinically, except in relation to rheumatism, and that in this disease the term "carditis" is sounder. The description of myocarditis, acute or chronic, as a separate disease with its special symptoms and signs, he asserted, needlessly complicates a general description of cardiac disease, which should remain essentially simple.

The main reason for the discrepancy between the histologic diagnosis of myocarditis and the failure to consider this condition clinically lies in the inability of the pathologist to make this diagnosis grossly If the heart is not examined histologically, the pathologist is often unable to diagnose myocarditis, the practicing physician, therefore, is not encouraged to make this diagnosis clinically Not only is myocarditis difficult to recognize on gross examination, but commonly a number of microscopic sections from various regions of the heart must be examined before an exact diagnosis can be made Such a thorough study often cannot be undertaken and as a result the diagnosis is missed For want of a positive diagnosis of myocarditis at autopsy and because of failure to explain the disease or death correctly on anatomic grounds, the clinician must resort to an explanation on the basis of disturbed function A clinical diagnosis of myocarditis is sometimes made, however, principally because the clinician had been taught the possibility of its existence

In this chapter, myocarditis in general will be discussed principally from an etiologic point of view. For a review of the older literature consult Monckeberg (1924) and Kirch (1927)

Incidence. Few references are available regarding the incidence of myocarditis.

Marcuse (1947) reported 36 instances of nonspecific myocarditis among 3800 autopsies. However, it was stated that the diagnosis was based on the microscopic examination of routine sections and that on the average only two blocks were cut in each case Excluded were instances of rheumatic heart disease, bacterial endocarditis, acute pericarditis, pyemic abscesses in the myocardium, specific granulomas and specific infections that are known to cause myocardial lesions, such as diphtheria and scarlet fever Brown and Hunt (1940) found acute myocarditis microscopically in 58 of 625 hearts from routine consecutive autopsies Albert (1938) studied 113 instances of various acute infectious diseases Myocarditis was noted in 46 At Michael Reese Hospital, among 5626 autopsies from which routine histologic sections were examined (Saphir, 1942a) myocarditis was found 240 times (4 3 per cent). Among 1000 other consecutive autopsies at the same institution, when more than the usual number of blocks (about 25) were taken from each heart for microscopic section (unpublished study), myocarditis was observed 90 times (9.0 per cent). A total of 1402 cases of myocarditis was reported from the Armed Forces Institute of Pathology by Gore and Saphir (1948). As Moritz and Zamcheck (1946) stated, the total number of autopsies recorded at the Armed Forces Institute of Pathology between January, 1942 and January, 1946, when practically all of these 1402 cases were observed, amounted to more than 40,000 Of the 1402 cases, 130 had rheumatic heart disease It is noteworthy that the cardiac condition in more than 90 per cent of the cases in this series was nonrheumatic Table IX-15, taken from Gore and Saphir, records the diseases found to be associated with myocarditis.

TABLE IX-15

Diseases Associated with Myocarditis * (From Gore and Saphir, 1948)

	Column 1	Column 2		Column 1	Column 2
Rickettsial diseases			Septicemia		
Scrub typhus	227	227	Streptococcus	11	23
Epidemic typhus	23	48	Staphylococcus	34	107
Rocky Mountain spotted fever	9	19	Pneumococcus	9	18
Diphtheria	144	221	Other acute bacteremias	15	Unknown
Subacute bacterial endocarditis	208	208			
Rheumatic heart disease	130	130	Acute glomerulonephritis	14	160
Meningococcemia	111	256	Acute tonsillitis	12	Unknown
Scarlet fever	24	44	Acute nasopharyngitis	41	Unknown
			Cellulitis, lymphangitis, and wound infections	13	Unknown
Weil's disease	7	8			
Relapsing fever	6	11	Tularemia	1	16
Syphilis (gummatous)	2	66	Brucellosis	2	4
			Miscellaneous (postinfectious)	13	Unknown
Chagas' disease	1	1			
Schistosomiasis	5	41	Exfoliative dermatitis	7	44
Malaria	5	135	Arsenical reaction	1	18
Trichinosis	2	2	Sulfonamide hypersensitivity	105	Unknown
Acute encephalitis	13	144	Disease unknown (so-called "idiopathic")	43	
Poliomyelitis	13	94			
Infectious mononucleosis	6	9	Starvation	33	50
Measles					
Guillain-Barré syndrome	3	30	Heat stroke		
Mumps	1	8	Surviving less than 24 hours	16	45
Epidemic hepatitis	1	400	Surviving more than 24 hours	13	23
Smallpox	1	9	Carbon monoxide poisoning (limited to patients who survived for an appreciable interval after the lethal exposure)	1	30
Virus pneumonia	32	222			
Tuberculosis	9	581			
Boeck's sarcoid	3	12	Emetine	1	70
Coccidioidomycosis	11	48	Burns	11	45
Blastomycosis	2	5			
Actinomycosis	1	9			
Torulosis	1	6			
			Total	1402	

* The figures in the first column represent the number of times myocarditis was encountered. Wherever possible the number of cases of each disease, screened to ascertain the first figure, is given in Column 2. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

Ages. Among the 90 instances of myocarditis mentioned above, which were found in 1000 consecutive autopsies, only eight were associated with endocarditis. The age distribution was as follows.

Ages in Years	*Number of Cases*
Less than 1	3
1-10	12
11-20	3
21-30	8
31-40	11
41-50	12
51-60	10
61-70	20
71-80	8
81-90	3

It is interesting that 31 instances were encountered in the age group from 61 to 90 years, an age period in which myocardial changes resulting from vascular disease are extremely common. There were 47 males and 43 females. Among Marcuse's (1947) 36 patients there were 26 males (72 per cent) and 10 females; the percentage of males in his entire autopsy material of 3800 cases was 65 The ages of these patients ranged from one month to 86 years Twenty-two patients were below the age of 40, and eight of these were less than 15 years old

Unexpected Death in Myocarditis. There are a number of communications on record stressing unexpected deaths from myocarditis Lisa (1939) studied 41 patients who died unexpectedly as a result of myocarditis. Wuhrmann (1939) in his monograph commented on unexpected deaths in patients with myocarditis. Among 60 patients studied by Saphir and co-workers (1944) nine had died unexpectedly Single instances of unexpected death have been reported by Helwig and Wilhelmy (1939), by Coulter and Marcuse (1944) and many others. Moritz and Zamcheck (1946) reported death from acute heart failure in 14 soldiers with acute and subacute (isolated) myocarditis, 10 of the 14 died within a few minutes after an unexpected syncopal attack. Glatthaar (1946) expressed the belief that foci of inflammation around vital branches of the coronary arteries or within the conduction system may be responsible for cardiac symptoms as well as for electrocardiographic changes and occasionally also for sudden death

CLASSIFICATION

Brown and Hunt (1940) classified myocarditis as acute, syphilitic and tuberculous. Acute myocarditis was subdivided into nonspecific and rheumatic types.

Vischer (1924) classified myocarditis as acute circumscribed interstitial inflammation (including abscesses of the myocardium) and acute diffuse interstitial inflammation The latter may be nonspecific as in infectious diseases, or specific as in rheumatic fever, pertussis, tuberculosis or syphilis, it may be the principal disease or an incidental condition in other diseases, as in tonsillitis or in phlegmonous inflammation without sepsis, or an isolated acute diffuse myocarditis. This last group is subdivided according to whether the blood culture is positive or negative. Marshall (1942) classified infective myocardial disease into (1) specific myocarditis (rheumatic fever, tuberculosis, gumma), (2) nonspecific, toxic (diphtheria and other fevers), (3) septic, and (4) isolated myocarditis Candel and Wheelock (1945) classified infectious myocarditis as (1) specific myocarditis (rheumatic fever, tuberculosis, syphilis); (2) nonspecific myocarditis (a) of known etiology, as diphtheria, tonsillitis, typhus, bronchiectasis, or clinical entity of undetermined etiology, such as infectious mononucleosis), (b) of unknown etiology (Fiedler's myocarditis); and (3) septic myocarditis (septicemia and associated subacute bacterial endocarditis).

For didactic purposes, a classification of myocarditis is presented in Table 1

TABLE IX-16

Classification of Myocarditis

"Fetal myocarditis"

Myocarditis following infectious and contagious diseases (as bacterial, virus, fungus, helminthic)

With endocarditis

Without endocarditis

Isolated myocarditis

Diffuse (sometimes the result of hypersensitivity)

Granulomatous (cause as yet unknown)

Specific myocarditis *

The defect in such a classification is immediately obvious. It is not free from the criticism of overlapping Thus, gonococcic and meningococcic myocarditis may or may not be associated with endocarditis; and rheumatic myocarditis may be classified as a specific myocarditis or as a form of myocarditis that may follow endocarditis.

The above classification is partially etiologic Jaffé (1944) believed that such a classification in relation to accompanying infection was valuable clinically but rather unsatisfactory pathogenetically. He suggested that in the light of genesis only two groups of myocarditis can be distinguished: (1) those in which the organisms are actually present in the myocardium and produce tissue reactions, such cases include myocarditis of septicemia, tuberculosis, and gummas, and (2) those in which the myocardium is free from the organisms but is indirectly influenced by the organisms at distant sites, as in diphtheria.

It might be mentioned in this connection that Jaffé often remarked that myocarditis occurs frequently. Thus, in 5000 autopsies performed in Venezuela, he encountered 500 cases of myocarditis (1946). Most of these disclosed the same histologic picture. He emphasized that only the muscle damage is a direct consequence of the underlying disease. This damage may be caused by various extrinsic agents, such as bacteria or parasites, or by intrinsic agents, as in metabolic disturbances. He further stated that it is a tenable assumption that the body may react similarly to various causes, especially if the etiologic agent affects the parenchymatous cells or organs, and if these damaged cells produce further reaction as a result of faulty secretion and absorption of products of cellular disintegration. Furthermore, in many illnesses the pathologic process may be the result not of a single transitory insult, but often, of continued and repeated insults. Thus another factor is added, namely, the allergic reaction of the individual, which in itself gives rise to various tissue changes. He concluded that chronic myocarditis is to be regarded as a uniform process in which there is, primarily, damage to the cardiac muscle fibers and, secondarily, mesenchymal alterations with cellular infiltrations. This process, although purely inflammatory, must be distinguished from all those myocardial inflammations in which organisms are present *in situ*, it is the result of the allergic reaction of the previously damaged cardiac muscle. The myocarditis in syphilis, schistosomiasis, and ankylostomiasis, he believes, is of this type

This concept of myocarditis will be further discussed in relation to isolated myocarditis. It may be mentioned here that so-called allergic myocarditis or myocarditis in hypersensitivity presents microscopically a more or less well-defined entity (French, 1946, Rich and Gregory, 1943a and b) which often is quite characteristic microscopically, and which does not always conform to Jaffé's description.

FETAL MYOCARDITIS

Reports of fetal (congenital) myocarditis, except in congenital syphilis, are exceedingly rare. Such reports are found chiefly in the older literature (Abbott,

* "Specific" indicates changes which histologically are so characteristic that a diagnosis of the cause can be made from the morphologic picture alone without recourse to bacteriologic studies, e g., rheumatic, tuberculous, syphilitic (gummatous)

1926) and usually are concerned with myocardial changes in hearts showing congenital anomalies. Gross (1941) stated that the valvular changes in instances of so-called congenital endocarditis (see page 766) are not the result of inflammation but signify the persistence of an early developmental stage of the involved valve. He also added that myocardial lesions seen in such hearts are not inflammatory in origin but represent healed, bland infarcts. Saphir and associates (1944), in studying 78 congenital anomalies of various types exclusive of minor anomalies such as a patent foramen ovale and patent ductus arteriosus, found an increase in connective tissue in several hearts but no inflammation, either acute or chronic

It is known that many children with severe congenital cardiac anomalies get along fairly well, though occasionally one may die unexpectedly. Intriguing as it may be to assume that myocardial changes are the direct cause of death in these children, a careful histologic study of such hearts usually discloses no evidence of any anatomic lesions in the myocardium to which death can be attributed.

One rather unusual instance was reported by Morison (1948), in which a child with tetralogy of Fallot died during a short-circuiting operation At autopsy, death was attributed to myocarditis. Froboese (1932) found severe myocardial fibrosis in a six-month-old infant which he interpreted to be the result of a congenital myocarditis (fibrosis myocardii congenita). There were no congenital anomalies.

Recorded instances in the literature of so-called idiopathic enlargement of the heart are definitely not the result of inflammatory changes of the myocardium. Some of these have been found associated with "status thymicolymphaticus" while others are classified as a glycogen infiltration (von Gierke's disease).

From the literature and from studies of the myocardium of a number of hearts with congenital anomalies observed in this laboratory, it must be concluded that, with the exception of myocarditis in congenital syphilis, fetal or congenital myocarditis, if it occurs at all, is extremely rare.

MYOCARDITIS IN INFECTIOUS AND CONTAGIOUS DISEASES

Myocarditis Associated with Acute Nasopharyngitis and Acute Tonsillitis. The literature contains reports of myocardial damage resulting from tonsillitis. Most of these, however, are clinical, some presenting changes in the electrocardiogram as evidence of myocardial damage.

Wuhrmann (1939) considered chronic tonsillitis as a type of infection which may be responsible for myocarditis. Scherf and Boyd (1939) emphasized repeatedly that commonly focal infections, such as those of chronic tonsillar infection, cause myocarditis Scherf (1940) reported five nonfatal cases in which myocarditis followed acute tonsillitis. He remarked that in his experience this complication occurred in 10 to 15 per cent of such cases Candel and Wheelock (1945) included one patient with peritonsillar abscess in their series of nonfatal cases and described one fatal case with autopsy in which myocarditis, following acute tonsillitis, was observed

In a study of the pertinent material available at the Armed Forces Institute of Pathology, reported by Gore and Saphir (1947), there were 35 instances of nonrheumatic myocarditis in association with upper respiratory infections. The portal of entry in 12 of these was acute tonsillitis and in 23, acute nasopharyngitis. Septicemia was not believed to be of etiologic importance, since significant visceral alterations were absent in all 35 cases.

Corynebacterium diphtheriae was absent from the culture material and diphtheria had been excluded clinically in each instance. The cause of death was determined to be cardiac failure in all cases. Fifteen of the patients had died unexpectedly. Grossly the hearts were soft, flabby and friable. The myocardium was pale, gray or streaked with gray, or mottled with red or yellow. Petechial hemorrhages were found subepicardially seven times and diffusely scattered throughout the myocardium three times. Mural ventricular thrombi were encountered in one case. Five of the hearts were regarded as grossly normal.

Histologically, the changes in the myocardium were striking. The lesions varied from circumscribed focal areas of inflammation, principally involving the interstitial tissues, to areas of diffuse inflammatory infiltration associated with necrosis of muscle fibers The inflammatory cellular response was predominantly and characteristically mononuclear. In the most cellular zones, lymphocytes outnumbered the other elements, which included mononuclear cells larger than lymphocytes with densely stained nuclei, polymorphonuclear leukocytes and Aschoff cells. Aschoff cells, though they constitute parts of the Aschoff body, are often found in various types of myocarditis and *per se* are neither characteristic of any specific lesion nor are they pathognomonic of rheumatic fever. They are characterized by an abundant, faintly basophilic cytoplasm, a lightly stained oval nucleus, a thin sharp nuclear membrane and a characteristic arrangement of the chromatin in the form of a central bar or node from which weblike processes extend toward the periphery. Aschoff cells are also known as "myocytes," because of Anitschkow's (1913) original interpretation, and as myocardial reticulocytes (Ehrlich and Lapan, 1939).

Endothelial leukocytes (histiocytes) and Aschoff cells were frequently found in small accumulations about a few intensely acidophilic, homogeneous muscle fibers, and sometimes infiltrated the interstitial tissues more diffusely, especially subendocardially about the orifices of the thebesian vessels. The focal cellular accumulations around a few necrotic muscle fibers appeared to represent a very early and rapid morphologic change which Gore and Saphir named "explosive lesion." Plasma cells and eosinophils were found in varying numbers, and in older lesions fibroblasts were observed. Mast cells were present, as they are normally, but did not appear to participate to any extent in the inflammatory reaction. Bacteria were absent from all sections examined. The inflammatory cells were accompanied by exudation of variable quantities of protein-rich fluid in the interstitial tissue. The lesion involved both the scanty stroma within the muscle fasciculi and the more abundant stroma accompanying the blood vessels in the interfascicular septa.

It is thus evident that myocarditis is occasionally associated with acute nasopharyngitis and acute tonsillitis Yet, reported autopsy cases are exceedingly rare; Candel and Wheelock (1945) stated that they believed that their report of acute nonspecific myocarditis following acute tonsillitis was the first recorded case proved by autopsy. The myocarditis is principally interstitial in type; the cellular reaction is predominantly mononuclear but significant numbers of polymorphonuclear leukocytes also accumulate at sites of severe inflammation

Myocarditis in Pneumonia. Relatively few references are found in modern literature to myocarditis in pneumonia.

Stone's studies (1922) are usually quoted. He examined microscopic sections of the myocardium in 34 instances of lobar pneumonia and in 37 instances of bronchopneumonia. Polymorphonuclear leukocytic and round cell infiltrations were found in



Figure IX-45 Myocarditis in late pneumonia. Note presence of lymphocytes and only a few polymorphonuclear leukocytes within the interstitial tissue Hematoxylin and eosin X 125

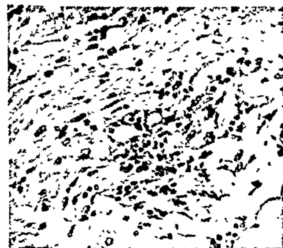


Figure IX-46 Myocarditis in subject with organizing pneumonia Note the many monocytic cells Iron-hematoxylin X 300

8.9 per cent, and outspoken interstitial myocarditis in 2 9 per cent of the patients with lobar pneumonia Among the patients with bronchopneumonia, polymorphonuclear leukocytic and round cell infiltrations occurred in 10 8 per cent and interstitial myocarditis in 2.7 per cent. Neuhoff (1914), Liebmann (1915), Berry (1920), Roesler and Soloff (1935), Swift and Smith (1937), and Spühler (1942) reported isolated instances of myocarditis in pneumonia Saphir and Amromin (1948) studied 67 hearts of patients with bronchopneumonia in which the inflammation of the lung had involved at least one entire lobe Twenty-six or 38 8 per cent of these revealed inflammatory changes sufficient to warrant the term "myocarditis" (Figures IX-45 and IX-46), 15 of the 26 were classified as acute myocarditis, three as acute serous, and eight as subacute myocarditis The outstanding clinical criteria pointing to the diagnosis were found to be: disproportion between the pulse rate and the temperature, drop in the arterial blood pressure, cyanosis out of proportion to the apparent pulmonary involvement, and unexpected death Six of these 26 patients exhibited electrocardiographic abnormalities. The authors emphasized the necessity of examining multiple sections of the myocardium either to establish or to disprove a diagnosis of myocarditis Among 240 instances of myocarditis studied by Saphir (1942a), myocarditis was found in association with lobar pneumonia 7 times, and with bronchopneumonia 19 times.

Myocarditis (Figure IX-47) is also encountered in instances of so-called acute *laryngotracheobronchitis*. Saphir (1945a) reported unexpected death in five children The autopsies disclosed severe laryngeal edema and edema of the epiglottis and subglottis, with absence of any obstructing (pseudo)membrane Grossly, the hearts were dilated, and microscopically the myocarditis was principally interstitial in dis-

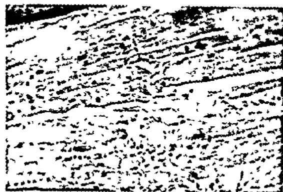


Figure IX-47 True chronic myocarditis. Note the fibrosis combined with inflammatory cells. Iron-hematoxylin. X 250.

tribution. The most commonly encountered inflammatory cell was the lymphocyte. Neutrophils were rarely present Three of these five instances disclosed, on microscopic examination, early bronchopneumonia which was not recognized grossly.

Fatal myocarditis also occurs in instances of *bronchiectasis*. Jex-Blake (1920) mentioned that three of 110 patients with bronchiectasis died of heart failure. He apparently referred to right ventricular hypertrophy with ultimate right heart failure. Ogilvie (1941) stated that myocardial damage occurs as a late result of chronic sepsis Chafee, Ross and Gunn (1942) described myocarditis in a patient who died suddenly after an asthmatic attack. The myocardium was massively infiltrated with eosinophils, polymorphonuclear leukocytes, a few lymphocytes, and plasma cells, and also contained small foci of necrosis Bronchiectasis was found in 152 of 6257 autopsies (Saphir, 1943). Myocarditis was encountered in eight of these 152 autopsies. In three the myocarditis was recent, but complicated by myocardial fibrosis in one of the cases, and associated with an aneurysm of the heart in another. Subacute myocarditis and true chronic myocarditis were each present twice Three of these eight patients had died unexpectedly

Myocarditis in Whooping Cough (Pertussis). The older literature includes whooping cough as a causative factor in myocarditis (Kirch, 1927).

Oberndorfer (1914) demonstrated myocarditis in a seven-year-old girl who died unexpectedly a few weeks after having contracted whooping cough. There were many infiltrations of round cells throughout the myocardium. Among 27 instances of myocarditis reported by Vischer (1924), one patient with whooping cough had an interstitial myocarditis with predominating lymphocytes and a few leukocytes and plasma-like cells. Brick (1913) studied microscopically the hearts of seven patients with whooping cough. In one (Case 7) a few leukocytes and small accumulations of round cells were present; in another (Case 12) occasional leukocytes were encountered throughout the myocardium. In general, hypertrophy of the right ventricle was the main cardiac abnormality.

Influenza. Myocarditis from virus infection will be discussed later. The literature contains a number of instances in which myocarditis was thought to have been the result of infection with *Hemophilus influenzae* or of infections loosely called "flu" or "grippe." A number of these reports are not detailed enough to warrant the conclusion that the myocarditis had been caused by a definite organism.

It may be mentioned that of 27 persons with fatal influenza (virus infection?) in the epidemic at Camp Devens in 1918 reported by Wolbach and Frothingham (1923), the myocardium of only one revealed small areas of cellular infiltration consisting chiefly of mononuclear cells with a few polymorphonuclear leukocytes and mast cells. Schmorl, according to Kirch (1927), was the first to refer to myocarditis in patients dying during the epidemic of "grippe" in Europe in 1918. Miller and Branch (1923), and DeSanto and White (1933) described myocardial changes in a *Hemophilus hemolyticus* infection. Lichty (1937) found myocarditis caused by a hemolytic parainfluenza bacillus. Craven, Poston and Orgain (1940) also reported myocarditis in two instances of endocarditis caused by *Hemophilus parainfluenzae*.

Diphtheria. Myocardial damage is a well known and sometimes fatal complication of diphtheria. The literature up to 1940 has been reviewed by Saphir (1942). Ch'in and Huang (1941) gave a general review of the histologic lesions of the myocardium in diphtheria. Warthin (1924) presented an analysis of the findings in 17 diphtheritic hearts stating that the essential lesion was toxic parenchymatous



Figure IX-48 Myocardium in early diphtheria Note area of degeneration and early necrosis but absence of true myocarditis Hematoxylin and eosin X 100 (WCGH, 45 P 191 L)

hyaline degeneration or necrosis (Figure IX-48), often with fatty infiltration. He indicated that a reparative inflammatory process (myocarditis) develops later. Whether the term "myocarditis" is justified, in speaking of a reparative inflammation, is questionable Unfortunately, other investigators have used the term myocarditis, not to denote simple reparative inflammation, but to signify a primary myocardial inflammation in diphtheria Nuzum (1919) had described an eosinophilic myocarditis in diphtheria

Gore (1948) reported the findings from autopsy records and microscopic slides of 221 fatal cases of diphtheria, of which 205 were available for study. Myocarditis alone was encountered in 99 instances. Myocarditis with neuritis was reported 44 times, the presence of neuritis being determined solely from the clinical records, whereas the diagnosis of myocarditis was based on microscopic findings Gross cardiac abnormalities were reported in 71 per cent of the cases. Dilatation of the chambers, flaccidity, pallor, and "streakiness" of the myocardium, noted singly or in combination, were the changes most frequently reported The extent of the microscopic changes varied from severe involvement with large and multiple areas of muscle damage to minor changes with only occasional small foci of involvement No organisms were demonstrable microscopically in any of the sections examined Gore emphasized that the diphtheritic infection produces a varying degree of parenchymal damage, manifested as segmental hyaline, granular and fatty degeneration of the muscle fibers. The secondary inflammatory response of the stroma appears, at first, to consist largely of locally developed histio-

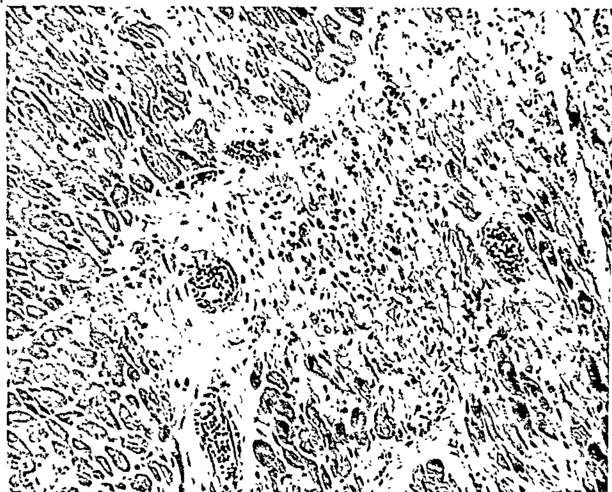


Figure IX-49 Area of necrosis with myocarditis in diphtheria. X 100 (Courtesy, Armed Forces Institute of Pathology, Acc 152,452.)

cytes, but it is soon augmented by an influx of plasma cells and lymphocytes. Degenerated muscle is destroyed, leaving gaps and defects in the myocardium which, if the length of survival permits, heal by fibrosis (Figure IX-49) The muscle showed only abortive regeneration. Statements by Anitschkow (1913), Heller (1914) and Warthin (1924) to the effect that there is true muscle regeneration were based on Anitschkow's belief in the myogenic character of the "myocyte," a cell now generally regarded as having a histiocytic function. In one-third of the cases the manifestations of myocarditis appeared at a time when the patient seemed to be well on the way to convalescence. The interval between clinical manifestation of diphtheria and the onset of cardiac symptoms has been designated as "the deceptive interval" of apparent improvement.

Greene (1946) believed that the myocardial changes in his case were caused by a combination of sulfonamides and diphtheria toxin. Cloudy swelling, simple necrosis, and granular fragmentation, he thought, were characteristic of myocardial involvement in diphtheria. The interstitial reaction, the round cell and polymorphonuclear leukocytic infiltrations and the fibroblastic proliferation he believed to be secondary to these diphtheritic effects. On the other hand, the presence of large pale mononuclear cells with eosinophilic cytoplasm was believed to be representative of sulfonamide medication. He con-

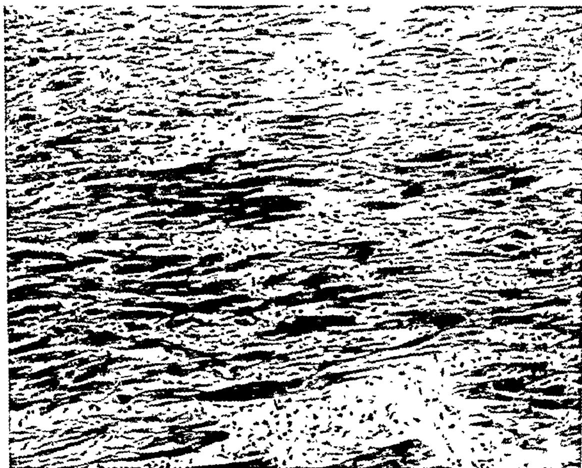


Figure IX-50 Healing myocardial changes in diphtheria Note early replacement fibrosis X 70 (Courtesy, Armed Forces Institute of Pathology, Acc 143,672)

cluded that the usual hazards of sulfonamide therapy are increased when the heart is already damaged by diphtheria or other toxins

Myocarditis has also been reported as a complication of cutaneous diphtheria (Solomon and Irwin, 1947) Kay and Livingood (1946) found evidence of myocarditis in four patients among 140 with cutaneous diphtheria; one of the four died. These authors were impressed with a definite parallel relationship between the severity of the cutaneous lesions and development of cardiac complications.

As a result of the myocardial changes in diphtheria, fibrosis and hyalinization may ensue (Figure IX-50). Occasionally, instances of calcification of the heart muscle fibers have been reported.

Ceelen (1919) stated that the toxin of *Corynebacterium diphtheriae* may produce parenchymatous degeneration and at times even calcification of the myocardium He observed partial calcification of the fibers of the right bundle branch and also calcification within the myocardium Kratzeisen (1920) observed deposition of calcium within the diseased muscle fibers of the heart of a patient who died of diphtheria. Edelstein (1940) observed massive calcification with ossification in the myocardium of an 11-year-old boy. Though no definite etiology for this lesion was evident it seemed that either diphtheria or infection with *Hemophilus influenzae* produced degenerative changes and necrotizing le-

sions of the heart muscle with secondary calcification. The heart was the only organ in the body which showed calcification.

Heart block is often encountered in diphtheria. Only Kocher's study (1947) will be mentioned here. At autopsy, he found, in a diphtheritic patient with complete heart block, diffuse destruction of muscle fibers within the interventricular septum. These fibers were surrounded by infiltrations of neutrophils, lymphocytes, monocytes and a few plasma cells; the process had extended into the junctional tissues between the atrium and ventricle.

Also on record are a number of instances of myocardial changes, the result of injection of toxins of *Corynebacterium diphtheriae*. Gukelberger (1936) produced myocardial lesions in 24 of 28 guinea pigs by injecting diphtheria toxins (0 0006 Gm. per 100 Gm. of body weight). The animals died at the following periods after injection: 4, three days; 1, four days, 3, five days; 2, six days, 3, seven days; and 3, after nine days. Twelve animals were sacrificed on the eleventh day. In 24 of the 28 animals the myocardium showed changes which were diagnosed as diphtheritic myocarditis, though in some instances only simple fatty degeneration was noted The animals that died early showed principally degeneration and evidence of myolysis. The animals that died later showed varying degrees of true inflammatory changes. Often, transitions from degenerative to inflammatory stages were noted. The earliest and the most severe lesions were encountered principally in the middle-ring musculature of the heart close to the apex.

Scarlet Fever. Stoeber (1935) examined the hearts of 22 patients who died of scarlet fever. The ages ranged from five months to 28 years, only one patient was older than 28 (50 years old). Six hearts had no microscopic changes and in four the changes were minute. The other hearts disclosed various amounts of cellular infiltration (Figure IX-51). Particularly prominent were faintly-stained large oval cells without recognizable cytoplasm, the large nuclei of which showed fine ramification of the chromatin. These cells were obviously Aschoff cells. Stoeber emphasized that the myocarditis of scarlet fever and that of diphtheria are quite different, diphtheria producing primary degenerative changes in the parenchyma. Hemorrhages in the conduction system may be the cause of unexpected death in scarlet fever. Stoeber also remarked that the same patient may have scarlet fever and rheumatic fever and both types of myocarditis. The latter remark is interesting and recalls Schmorl's findings (1914) of typical Aschoff bodies in the heart of a two-year-old child who died of scarlatinal myocarditis. He emphasized the fact that there was no history of rheumatic fever.



Figure IX-51 Post-scarlatinal myocarditis X 100 (WCGH, 45 P 173)

Fahr (1921), apparently stimulated by Schmorl's statement, studied the hearts of 9 patients who died as a result of scarlet fever. In four patients the diagnosis of myocarditis had been made clinically. In not a single instance were rheumatic nodules (Aschoff bodies) found in the

myocardium However, minute granulomas were present, they were particularly noticeable around the small blood vessels These nodules were much smaller than Aschoff bodies and no giant cells were seen. Four of the 9 hearts also had endothelial cell proliferation of the endocardium in the form of small nodules In three other hearts only a few such nodules were found, and in two they were absent. Kirch (1927), discussing Fahr's studies, concluded that the rheumatic nodules (Aschoff bodies) are specific lesions, occurring in no other disease, and must be well separated from the nodules seen in scarlet fever Fahr (1930), a few years later, studied the heart in 11 cases of scarlet fever He emphasized that in one instance a severe myocarditis was present. The most commonly encountered change was *subendocardial proliferation in the form of minute nodules.* In two instances they were marked, in three they were less conspicuous, in four only a few were present and in two they were absent.

Magladery and Billings (1936) emphasized *the difference in intensity of myocardial involvement in the various scarlet fever epidemics* Among 37 instances they found 29 with myocarditis, which sometimes was rather slight in extent. However, by using the oxidase reaction they clearly *demonstrated an increase of granulocytes.* In one heart perivascular infiltrations were encountered which resembled Aschoff bodies. This heart also showed an acute verrucous endocarditis

Brody and Smith (1936) studied the visceral lesions in scarlet fever and related streptococcic infections, in a series of 44 patients with scarlet fever and of 15 patients with possible scarlet fever the hearts were examined microscopically They stated that lesions of varying severity occurred in over 90 per cent of the hearts, the chief cell being some form of round cell These lesions fell into three overlapping types: (1) either a focal or a diffuse interstitial infiltration of the myocardium, having no apparent distribution with reference to the cardiac blood vessels and usually seen in conjunction with either of the following two types; (2) an infiltration either in or about the smaller coronary arteries which took the form of arteritis or periarteritis in which the invading cells were mononuclear, although in some cases there was a slight admixture of neutrophilic polymorphonuclears and rarely eosinophils; (3) the commonest type, consisting of a subendothelial infiltration which sometimes occurred beneath the endocardium of the ventricular chambers but was most striking in the walls of the thebesian vessels.

In summary, it seems that myocarditis associated with scarlet fever is not rare. The *inflammation is characterized principally* by an involvement of the interstitial tissue, though the cardiac muscle fibers may be replaced by inflammatory cells. The cells most commonly encountered are lymphocytes, which may be distributed *perivascularly in the form of minute nodules.* Circumscribed proliferations of endothelial cells are encountered relatively often in subendocardial regions.

Myocarditis in Meningococcal Infections. To judge from the relevant literature, *myocarditis is rarely caused by meningococci* Case reports of meningococcal endocarditis disclose an accompanying myocarditis more often than might be expected. Reports of meningococcal myocarditis in the absence of endocarditis, however, *are quite rare, apparently* because many sections of myocardium of patients dying of meningococcemia are not regularly examined.

Saphir (1936) examined the heart in 10 instances of meningococcemia and reported *myocarditis in two* This myocarditis was characterized by hemorrhagic exudate with the presence of endotheli

leukocytes and a few polymorphonuclear leukocytes, some of which contained gram-negative diplococci. Ferguson and Chapman (1948) examined the heart in 16 cases of acute fulminating meningococcic infections and described inflammatory cells in the myocardium in 12. The inflammatory exudate consisted of varying numbers of mononuclear leukocytes, in addition, occasional foci of necrosis were encountered. Epstein and associates (1947) also wrote on meningococcic myocarditis.

Moritz and Zamcheck (1946) studied 350 cases of fatal meningococcic infections reported by the Armed Forces Institute of Pathology. In 110 of these patients death occurred within 24 hours after the onset of incapacitating symptoms Myocarditis (myocardial exudation) was observed in 37. In 14 instances postmortem examinations disclosed no significant pathologic changes other than myocarditis. It is apparent from the histologic studies of these hearts that the diagnosis of myocarditis usually referred to an exudation of polymorphonuclear leukocytes superimposed on a monocytic reaction which might be focal or diffuse, and sparse or dense

It is well known that patients with meningococcemia having the so-called *Waterhouse-Friderichsen syndrome* may die unexpectedly. No pertinent references are found in the literature to the association of meningococcic myocarditis with this syndrome. However, when reports of Waterhouse-Friderichsen syndrome are scrutinized it is found that myocarditis is sometimes described even though such reports do not include "myocarditis" in their titles. (See Saphir, 1949.) Because there are few references in the literature to myocarditis in the Waterhouse-Friderichsen syndrome, the following significant cases will be quoted.

In one instance of the Waterhouse-Friderichsen syndrome, Herbut and Manges (1943) found, immediately beneath the endocardium of the left ventricle, several sharply circumscribed hemorrhages which microscopically were composed of normal and laked erythrocytes. Occasionally the capillary walls and the immediately adjacent connective tissue were permeated with polymorphonuclear leukocytes. Small collections of polymorphonuclear leukocytes, dissociated from blood vessels, were also seen between the muscle fibers and in the supporting connective tissue. D'Agati and Marangoni (1945) studied the heart in five cases, in all five patients the microscopic changes were of a nonspecific character, similar to those found in other infectious diseases and in septicemias. Ikeda and Rosenthal (1945) reported two instances; in one they recognized a focal collection of polymorphonuclear leukocytes which, they stated, might lead one to suspect focal myocarditis. Newman (1945) recorded three instances of this syndrome. In the first, foci of neutrophilic leukocytes and a few large mononuclear cells were scattered widely through the myocardium; in a second case, the myocardium contained many polymorphonuclear leukocytes in the interstitium and a rare zone of myocardial necrosis. Holman and Angevine (1946) reported fulminating meningococcic septicemia in two patients, one having definite signs of circulatory collapse. One of these patients died and the autopsy disclosed widely disseminated areas of edema, capillary engorgement and degeneration of muscle fibers. The second patient survived, but electrocardiographic changes were noted. In a review of 29 autopsied cases of meningococcus infection, they stated that acute myocarditis was found microscopically in seven, and was associated with septicemia in six of these seven patients.

Kinsman and associates (1946) stated that the cause of the circulatory collapse, which is such a prominent phenomenon in this disease, has been the subject of much

speculation. It seems unreasonable to place the entire blame on the exhaustion of hormonal supply which is associated with the adrenal lesions, even though the latter are usually of high degree, as in the fatal cases reported here In certain instances, injuries of other organs may be responsible to a greater or lesser degree. In one of their patients, there was pulmonary edema and bilateral hydrothorax, consistent with circulatory failure of cardiac origin. On microscopic examination of the heart, degeneration of muscle fibers and polymorphonuclear and mononuclear leukocytic infiltrations of the connective tissue were observed It was believed that the myocardial changes were sufficient to have caused circulatory collapse. Wasserman (1946) stated that the viscera, aside from the adrenals, usually show no significant pathologic lesions, with the exception of acute cloudy swelling of the myocardium, the kidneys and the liver. Rappaport and Zuckerbrod (1945) reported a patient who had a fulminating meningococcal infection and stated that myocarditis had been proven by electrocardiography. It is interesting in this respect that Black-Schaffer and associates (1947) were able to produce occasional foci of acute myocarditis and necrosis in experiments designed to determine whether a relationship exists between the lesions of meningococcic purpura and the Shwartzman phenomenon.

From a review of these case reports of Waterhouse-Friderichsen syndrome, it thus appears that myocarditis has been occasionally noted as a complication. A fall of blood pressure, coincident with gallop rhythm, had been observed in one of these patients, and in another myocarditis was recognized clinically by means of electrocardiographic changes Myocarditis, believed to have been sufficient to cause circulatory collapse, had been noted in a third instance

Saphir (1949) found myocarditis in four patients with Waterhouse-Friderichsen syndrome Two of these patients were dead on arrival at the hospital and the other two died four and seven hours, respectively, after admission Hemorrhages in the skin and throughout both adrenals were found in all four patients.

It is important to note that at times myocarditis may be associated with meningococcal meningitis or meningococcemia, and that such associated myocarditis, with resulting myocardial failure, will seriously influence the prognosis in meningococcal meningitis, not only because of myocardial failure, but because the myocarditis is seemingly the result of an overwhelming infection with meningococci.

Among the 97 instances of myocarditis in children, studied by Saphir and coworkers (1944), there were four in which myocarditis was associated with meningitis. In two, myocarditis and meningitis were caused by *Hemophilus influenzae*, in one by streptococci, and in another by pneumococci.

Gonococcal Myocarditis. Gonococcal myocarditis, in the absence of gonococcal endocarditis, is extremely rare, myocarditis, however, is often found in association with gonococcal endocarditis Focal necrosis with abscesses seems to be the most commonly encountered lesion (Williams, 1938).

Sabathie (1935) remarked that in some instances of gonococcal infection that primary lesion within the heart was found in the interatrial and interventricular septum and that the heart valves were involved secondarily Abscesses were seen in the myocardium very close to the endocardium. Bang (1940) remarked that the possibility exists that gonococcal myocarditis may be a cause of chronic cardiac disease He also emphasized that in current textbooks on heart disease, gonorrheal infection is never mentioned as a possible cause of myocarditis Among Candel and

Wheelock's (1945) clinical series of patients with myocarditis were three with acute gonococcal arthritis

Salmonella Infections. Myocarditis in these infections is rare, while degenerative changes such as cloudy swelling and fatty degeneration are more often reported.

LeSage (1932) studied the hearts of patients who had died of typhoid fever. Grossly, the hearts were flabby; their consistency was compared to that of a wet towel. Microscopically, only fatty degeneration was noted Yet the microscopic diagnosis was acute myocarditis, although the reason for such a diagnosis does not seem clear. Kirch (1927) stated that myocardial changes in typhoid fever are far less common than one is led to believe from the older literature. Mamzer (1947) found, in 35 of 60 patients with typhoid fever, electrocardiographic abnormalities other than tachycardia and bradycardia. In 18 the changes persisted during convalescence and in one they first developed during this period He described cloudy swelling or hyaline degeneration of myocardial fibers with necrotic foci of minute size and scattered or focal interstitial infiltrations He remarked that the clinical picture of heart failure in typhoid myocarditis is different from heart failure in valvular disease in its quick development, and resembles myocarditis in diphtheria in the combination of "forward failure" and "backward failure." In serious cases the extreme weakness and apathy, the moist and cold lividity of the skin with low blood pressure and insufficient pulse pressure of the "forward failure" are combined with engorgement and tenderness of the liver, congestion of the lungs, cyanosis and sacral edema, the heart sounds are dull and often a systolic murmur is present at the apex; there is always tachycardia, often embryocardia, and sometimes gallop rhythm. He concluded that myocarditis is the cause of death in typhoid fever more often than is suspected. At the peak of the infection the myocarditis is easily overshadowed by the peripheral circulatory disturbance; the clinical manifestations of this myocarditis, tachycardia and circulatory instability after exercise, do not become manifest until convalescence and then persist for a longer time, in most cases, than the cardiographic alterations

It may be of interest to point out in this connection that Cornil and associates (1933) constantly found myocardial lesions in guinea pigs infected with the typhoid bacillus. The degenerative changes ranged from loss of the cross-striations of the muscle fibers to severe cloudy swelling. Within the connective tissue a nodular or streaky exudate, essentially formed by histiocytes, was present. These lesions were typically perivascular. Edema, hyperemia and small hemorrhages were also encountered The electrocardiogram showed disturbances of conduction.

Wells (1937) recorded an instance of acute endocarditis produced by *Salmonella paratyphi B* The myocardium microscopically showed many small foci of acute inflammation with necrosis of muscle fibers These often were located about fibrinous emboli. There were small areas of replacement of myocardium by young fibrous tissue. Also Meyer and Howell (1938) observed an instance of endocarditis caused by *Salmonella paratyphi B* in which the myocardium histologically presented foci of lymphocytic infiltrations with a few polymorphonuclear leukocytes and histiocytes

Nunes (1949) described a special type of myocarditis in typhoid fever with the presence of large mononuclear cells having pale nuclei with a fine reticulum pattern and basophilic cytoplasm. These lesions were found principally in the interstitial tissue and often just beneath the endocardium or pericardium. They were most

commonly present in the hearts of patients dying early in typhoid fever with intestinal lesions characterized by medullary swelling

Dysentery. In regard to the occurrence of myocarditis in patients with dysentery of any variety, Kirch (1927) stated that such a complication occurs occasionally. Knaack (1915) reported that a 20-year-old-soldier had signs of myocarditis a few weeks after having suffered an attack of Hiss-Y dysentery. There was no autopsy. It may be of interest to mention here that Duvernay and Gerbay (1929) observed a patient who died suddenly, presumably from myocarditis, after enterococcic infection.

Brucellosis. Perhaps not as rarely as one would be led to expect from the literature, myocarditis also occurs in brucellosis. Amuchastegui and Herrero (1948) described interstitial myocarditis in two such instances. Electrocardiographic changes had been noted clinically. The myocarditis appeared in the course of infection with *Brucella melitensis.* Attention was called to granulomatous lesions consisting of histiocytes, lymphocytes, plasma cells, fibroblasts, a few eosinophils and small capillaries. These granulomas were similar to those occasionally occurring in the skin.

Myocarditis in Pyemias. Weiss and Wilkins (1937b) stated that abscesses of the myocardium (Figure IX-52) are relatively rare and that the literature on this subject is meager. They remarked that, in most instances, such abscesses are metastatic manifestations of an overwhelming sepsis and that they are of more theoretic than clinical significance.

Among the necropsy reports of the Department of Pathology at the Boston City Hospital, abscesses in the myocardium were noted in 31 cases, with bacteriologic data available in 26. *Staphylococcus aureus* was responsible for sepsis in 20 cases, pneumococci in 2, *Streptococcus*



Figure IX-52 Acute suppurative myocarditis Iron-hematoxylin. X 250

viridans in 2, *Streptococcus pyogenes* in 1, and meningococci in 1. These authors give detailed autopsy findings in a 73-year-old white man. The pericardial cavity was filled with blood. There was a rupture of the right ventricle below the base of the pulmonic valve, over this area the myocardium was pale gray-brown and showed a few small irregular yellowish points Histologically, the ruptured area was surrounded by a marked diffuse neutrophilic infiltration of the pericardium and myocardium and acute necrosis of the heart muscle. The Gram-Weigert stain showed numerous gram-positive cocci in pairs and clusters in the abscessed area. Bacteriologic examination of the blood, obtained from the cardiac cavity, yielded a pure culture of *Staphylococcus aureus* These authors referred to reports of seven instances of rupture of the heart by abscess in which the descriptions were sufficiently detailed to rule out other conditions Flaxman (1943) stated that among 14,160 autopsies, myocardial abscesses were noted in 29. This, offhand, does not seem a significant number. However, one must take into consideration that abscesses are often small and that a number of sections of the myocardium must be cut and examined to determine the presence of abscesses. Thus, statistical reports on the presence or absence of abscesses in the

myocardium, taken from routine autopsy records, do not give the true incidence.

It may be of interest to mention here that among the 654 cases of spontaneous cardiac rupture collected and analyzed by Krumbhaar and Crowell (1925) abscesses were mentioned in only 3 and myocarditis in 4. Of 92 additional cases of ruptured heart analyzed by Davenport (1928), the rupture was the result of an abscess in 2. Sossai (1946) also described an instance in which rupture of the heart was caused by inflammation (abscess?) rather than infarct. Minute abscesses in the myocardium are also encountered in acute bacterial endocarditis and endocarditis lenta (see page 745).

Tularemia. Myocardial changes are also noted in tularemia Goodpasture and House (1928) described a moderate accumulation of large mononuclear cells about the vessels of the heart. Lillie and Francis (1936), in an exhaustive study on the pathologic character of tularemia, with a review of the literature, reported on histologic studies of the heart in 14 cases. In 9 it was substantially normal, except for a variable amount of transverse fragmentation of fibers. Finely granular, cloudy, swollen and poorly cross-striated fibers were seen in 3 instances, and in one a diffuse interstitial round cell infiltration was described.

Experimentally, they produced tularemia in the Belgian hare. Of 28 animals with acute tularemia, focal lesions composed of nuclear debris lying among intact heart muscle fibers were seen in only one animal. Among 61 rabbits with late acute and subacute tularemia, focal inflammatory lesions were present in 13. In 4 of these there were foci of lymphocytic infiltration and of interstitial caseous necrosis. In 5 others similar necrotic foci were present, some of which, however, were surrounded by interstitial proliferations of fusiform fibroblasts or vacuolated epithelioid cells and more or less lymphocytic infiltration. One of these 14 rabbits disclosed several granulating caseous foci in the wall of the left atrium. In the remaining 3 rabbits the focal lesions were typically granulomatous in character. Two of these 3 showed a few small perivascular nodules of epithelioid cells or fibroblasts with little necrosis and some lymphocytic infiltration. An area of dense interstitial proliferation of vacuolated epithelioid cells with atrophy and degeneration of muscle fibers was found in the ventricular wall. Also present were a few small foci of caseous necrosis and polymorphonuclear infiltration (see also page 811).

Foshay (1940) reported on his own large material and also reviewed the literature. He stressed the importance of previous heart disease as causing prolonged disability and death. However, cloudy swelling, loss of striations, fragmentation of muscle fibers and sparsely scattered focal cellular infiltrations between muscle bundles were associated with acute instances. These lesions were seldom severe or extensive and did not occur frequently. He thought that tularemia does not seriously damage the normal heart, but that it seems likely that this severe infection causes latent coronary disease to become manifest. In a report by Stump and Quinn (1940), the myocardium of one patient showed a slight increase of stroma and scattered small numbers of mononuclear cells, denoting active chronic myocarditis. A second patient with tularemia had as an incidental finding a number of active Aschoff bodies and evidence of chronic inflammation in the myocardium.

MYOCARDIAL CHANGES IN OTHER CONDITIONS

Myocardial Changes Associated with Glomerulonephritis, Uremia and Pregnancy

As early as 1879 Goodhart implicated the heart muscle as the cause of cardiac failure in acute glomerulonephritis. Whitehill and associates (1939) found clinical evidence of cardiac insufficiency in 71 per cent of their series of 138 patients with acute nephritis, microscopically, however, the heart muscle was almost always reported as being normal or, at most, slightly edematous Darrow (1941), however, reported finding separation of heart muscle fibers, perivascular accumulations and diffuse subendocardial infiltrations of mononuclear cells and a few plasma cells. Gore and Saphir (1948) reported the association of myocarditis in 16 of 160 fatal cases of acute and subacute glomerulonephritis. Excluded were cases of acute nephritis occurring subsequent to illnesses, such as scarlet fever, typhus and septicemia. The hearts were usually increased in weight and the muscle was soft and pale, with mottling or streaking. Microscopically, the inflammatory foci were small and involved only portions of a given section The serous components of the exudates were particularly conspicuous (Figure IX-53). The interstitial tissues were rendered more prominent by the presence of a faintly eosinophilic fluid and scattered inflammatory cells. Aschoff cells (Anitschkow myocytes) were often present but polymorphonuclear leukocytes were generally absent. Gore and Saphir remarked that their figure, 10 per cent of 160 cases, contrasts sharply with the high incidence of clinical myocardial failure reported by others They believed that the discrepancy is more apparent than real because of the patchy distribution of the inflammatory changes in the heart muscle and because routine sections of the myocardium examined in their study constituted but a small sample of the cardiac musculature

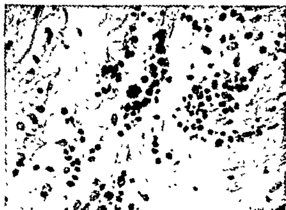


Figure IX-53. Myocarditis associated with uremia Note edema. Most of inflammatory cells are lymphocytes and a few resemble plasma cells Hematoxylin and eosin X 375

Bohn and Feldmann (1947) also emphasized the relatively frequent occurrence of myocarditis in patients with acute diffuse nephritis Myocarditis occasionally was the cause of death among German soldiers during World War II. The myocardial inflammation may not become evident until the fourth to sixth week of the nephritis.

It is well known that patients with uremia often have changes in the electrocardiogram. Luscher (1921) found a hemorrhagic type of myocarditis associated with acute fibrinous pericarditis in a patient with typical uremia and termed this "uremic myocarditis." Gouley (1940) stressed the existence of a specific uremic "myocardiopathy" but rejected the term "uremic myocarditis" He found, histologically, only fatty changes of the muscle fibers with hyaline degeneration and little or no cellular infiltration. Solomon and associates (1942) were unable to demonstrate any lesions characteristic of the uremic state in the hearts of 50 patients who died in uremia. An unusual endothelial hyperplasia of the cardiac arterioles

was present in 7 of 8 patients with acute necrotizing arteriolitis of the kidneys. On microscopic examination diffuse fatty degeneration with miliary myocardial necrosis was present. Acute interstitial myocarditis was found in 31 cases. Langendorf and Pirani (1947) concluded that the myocardial changes present were those attributed to the hypertensive heart disease with additional diffuse fatty degeneration, cloudy swelling of myocardial fibers and interstitial edema While the fatty degeneration was probably caused by concomitant anemia, the cloudy swelling and interstitial edema can be attributed to the uremic intoxication but cannot be regarded as diagnostic of uremia. They concluded that there was no evidence to support the existence of a specific so-called uremic myocarditis. The factors responsible for the changes in the electrocardiograms of patients with uremia are believed to be as follows. chronic left heart strain, myocardial changes due to coronary artery disease and diffuse pericarditis and changes in the electrolyte balance which give rise to hypocalcemia and hyperpotassemia.

Myocarditis supposedly occurring in *pregnancy* may be mentioned here for convenience. There are some references in the literature describing myocarditis in pregnancy. Most of these reports are clinical, with electrocardiographic changes.

Thus, Walls (1947) described such an instance in a 34-year-old woman with a pregnancy of three months' duration. The clinical diagnosis was toxic myocarditis. Szekely and Snaith (1947) studied the hearts in 19 unselected cases of toxemia of pregnancy. They concluded that cardiac involvement is a not uncommon complication of toxemia of pregnancy, some of the unusual types of heart failure occurring in late pregnancy and in the early puerperium. Some cases of postpartum vascular collapse may be instances of toxemia of pregnancy with associated myocardial damage. Their study is based on clinical investigations and electrocardiographic findings, but anatomic changes are not discussed.

Gouley and associates (1937) reported death in 3 patients from cardiac failure a short time following delivery. The myocardium of all 3 contained moderate numbers of lymphocytes and macrophages, and occasional neutrophils and eosinophils. Teel and co-workers (1937) and Hull and Hafkesbring (1937) reported similar cases with postmortem evidence of myocarditis. None of their patients had any valvular lesions.

Wallace and associates (1946) reported electrocardiographic changes in toxemia of pregnancy with cardiac failure. They believed that the electrocardiographic changes seen in these instances simulate those occasionally observed in acute nephritis. They stated that focal myocardial necrosis, edema, and cellular infiltration secondary to toxemia of pregnancy may give an electrocardiographic picture which simulates that of acute nephritis or of an atypical acute myocardial infarct. Melvin (1947) stated that "postpartal heart disease" had already been described by Virchow. He emphasized that in cases in which a postmortem examination had been made, a dilatation was found with slight hypertrophy of the heart and microscopic foci of necrosis

Blastomycosis, Actinomycosis and Yeast Infections of Myocardium

Blastomycosis. Kirch (1927) pointed out that rarely the heart may be involved in instances of generalized blastomycosis.

He cited the older literature but did not mention LeCount's report (1915) of a case in which about 100 miliary nodules were found in the epicardium. In this case histologic examination showed that only the superficial parts of the myocardium were involved. According to Baker and Brian



Figure IX-54 Coccidioidomycosis of myocardium Hematoxylin and eosin. X 375 (*Courtesy of Dr I M Reingold and The Williams and Wilkins Co, Baltimore Reprinted from Am J. Clin Path*, 20.1044, 1950)

(1937), Cleary in 1904 found minute blastomycotic nodules in the myocardium. Stober (1914) studied systemic blastomycosis and described lesions in the myocardium in his Case 6, but in the summary of his report he mentioned that myocarditis was found "in a few" Coupal (1924) found several abscesses in the left ventricle and the left atrium The wall of the abscess was made up chiefly of small mononuclear cells and basophilic giant cells. The abscess contained enormous organisms There was also diffuse infiltration by young fibroblastic cells Medlar (1927) reported instances of pulmonary blastomycosis, stressing the similarity of this condition to tuberculosis. The heart on histologic examination showed a small tuberculoid structure composed entirely of mononuclear leukocytes with three yeast-like bodies, resembling Torula. Baker and Brian studied 2 instances of blastomycosis of the heart. A firm nodule was present in the right atrium, the surface of which presented smaller elevations and ulcers. Histologically, just beneath the inner surface of the nodule, in the wall of the right atrium, were caseous areas containing blastomycetes The second heart showed large areas of necrosis containing numerous blastomycetes and comparatively few polymorphonuclear neutrophilic leukocytes Organisms were noted within the giant cells. Martin and Smith (1939) in a review of the literature on blastomycosis stated that the heart was involved in 9 instances, the lesion having been found in the pericardium, myocardium and endocardium They believed that it is possible for the cardiac lesions to develop by means of retrograde lymphatic extension. In a study of 13 cases of blastomycosis they mentioned 2 in which there were cardiac lesions. These were the cases described and discussed by Baker and Brian. (See also page 725.)

Actinomycosis. The rarity of cardiac actinomycosis may be inferred from the report by Sanford and Voelker (1925), who reviewed 670 cases of actinomycosis in the United States. In not a single instance was the heart involved Kirch (1927) also stressed the rarity of this condition, suggesting that the infection either may reach the heart as a result of hematogenous metastasis in instances of so-called generalized actinomycosis or may extend to the myocardium from a primary involvement of the neighboring structures. Primary actinomycosis of the organs of the neck also may extend to the mediastinum and thence to the myocardium

Kasper and Pinner (1930) cited 475 instances of actinomycosis, in 5 of which there was a record of myocardial involvement. Edwards (1931), discussing *actinomycosis in children*, reported that the myocardium of a 10-year-old boy contained numerous minute abscesses, particularly within the right ventricular wall. The actinomycosis was primary in the bronchioles and extended secondarily into the heart (*see also page 725*).

Torulosis. Crone and associates (1937) reviewed the subject of torulosis. Among the organs mentioned as being involved in torulosis were the central nervous system and *meninges*, lungs, liver, spleen, adrenal glands, kidneys, testes, abdominal, thoracic and axillary lymph nodes, bone marrow and periosteum. The myocardium was not mentioned as a site of infection.

Moniliasis. Polayes (1940) reported an instance of subacute endocarditis with systemic *moniliasis*. A cauliflower-like massive vegetation composed of monilia, leukocytes and fibrin situated on the posterior cusp of the aortic valve bulged into the right atrial wall, perforating at a point just above the medial cusp of the tricuspid valve. Acute interstitial myocarditis was also present.

Histoplasmosis. There are also instances on record of histoplasmosis of Darling (reticulo-endothelial cytomycosis) involving the myocardium and apparently causing myocarditis.

In Crumrine and Kessel's case (1931), the heart had a gelatinous coating with several vague white nodules suggestive of tubercles over the anterior surface near the base. However, microscopically the heart showed no organism. Dodd and Tompkins (1934) reporting an instance in an infant, stated that the parasites were demonstrated in all of the organs involved and in smears of the cardiac blood. Large mononuclear cells were found in practically all the tissues. The most conspicuous lesions were in the liver, lungs, spleen, lymph nodes and bone marrow. Humphrey (1940) reported 2 instances. In the first, microscopic examination of the myocardium showed several large areas in which there were cells packed with organisms, numerous plasma cells and what appeared to be immature lymphocytes. These areas were often so extensive as to cover a low-power field. The organisms (small coccoid dark-staining bodies with white haloes or capsules about them) were found in macrophages. In the second instance, no organisms were observed in the sections of the heart. Kuzma (1947) found interstitial myocarditis with granulomatous areas in which there were also macrophages containing Histoplasma. Menon and Rao Prasada (1945) recorded the presence of large caseous and conglomerate tuberculoid lesions situated near the junction of the septum with the pars membranacea, which had caused complete heart block; another lesion was present within the septum but situated closer to the apex.

For a discussion of myocarditis in parasitic diseases, see Chapter X.

The Myocardium in Rheumatoid Arthritis

Myocarditis in rheumatic fever has been discussed in Chapter VIII. Mention must

be made here, however, of myocardial changes encountered in so-called rheumatoid arthritis Unusual cardiac lesions associated with this disease were described by Baggenstoss and Rosenberg (1944) Focal collections of lymphocytes, plasma cells and reticular cells were scattered throughout the interventricular septum In two instances evidence of healed rheumatic myocarditis was inferred from the presence of perivascular "onion skin" scars However, more characteristic changes were found in the endocardium. The predominating structural unit of this inflammatory process was apparently a granulomatous body which is roughly spherical. The central zone consisted of an acidophilic, apparently necrotic tissue in which, however, a distinct reticular or collagenous framework was still recognizable. Adjacent to the necrotic center was a zone of large, elongated, radially directed cells with large pale-staining nuclei and faintly basophilic cytoplasm. The cells appeared to be proliferating extensively and many of them were multinucleated. The most striking features of these cells were their large size and their radial or palisade arrangement. Peripheral to the intermediate zone of palisaded cells was a broad and imperfectly demarcated zone of inflammatory reaction. Although it seems that these nodules were most often found in the endocardium, occasionally they also extended into the myocardium. In a report by Gruenwald (1948), the endocardium and muscular wall of the right atrium had been completely replaced in some areas by this granulation tissue. Mallory's stain for collagenous fibers and Gomori's method of silver impregnation revealed large numbers of fibers in all layers of the granuloma.

While not related to rheumatoid arthritis, the occurrence of myocardial changes in Libman-Sacks endocarditis, lupus erythematosus, dermatomyositis and scleroderma may be discussed here For a fuller discussion of changes in the myocardium in Libman-Sacks endocarditis, see Chapter on Endocarditis.

Myocardium in Libman-Sacks Disease Lupus Erythematosus Dermatomyositis and Scleroderma

Libman and Sacks (1923) in their description of a special type of valvular and mural endocarditis also found that the endocarditic process, microscopically, had invaded the adjacent myocardium rather deeply, with destruction and replacement of many muscle fibers. There were also foci of round cell infiltration and extreme fibrosis. Gross (1940) principally found vascular alterations in the blood vessels of the myocardium. Granular plugs were often seen in the lumens of the myocardial arterioles and venules (platelet thrombi). Also present were foci of interstitial inflammation consisting of polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells. He also described changes in *lupus erythematosus* in which the principal cells in the myocardium were plasma cells and peculiar large mononuclear cells, in addition to numerous histiocytes and fibroblasts. Klemperer and associates (1941) stated that in lupus erythematosus alterations of the collagen are often encountered in the myocardium. The fibers appear swollen and stain deeply with eosin, and usually infiltrations of lymphocytes are found. Fibrinoid degeneration and necrosis of the walls of small arteries are also encountered, but myocarditis is not common

Humphreys (1948) found focal myocarditis in most of the 21 cases of lupus erythematosus which she reported. In the mildest cases, the lesions were indistinguishable from minor scarring of rheumatic or arteriosclerotic disease, or were indeterminate small exudative lesions of doubtful significance. Obviously these may have been un-

related to the main disease. More significant were the fine scars, like those of small infarcts, the increased density of collagen along many or most of the intermuscular septa, and the thickened small arteries. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substance and fatty degeneration of myocardial fibers. No active rheumatic lesions were seen.

Kinney and Maher (1940) made an extensive study of two patients with *dermatomyositis*. In one of their patients the left ventricle showed muscle fibers separated by edema. Imperceptibly merging with the relatively uninvolved myocardium was an area in which the edema was more marked and in which lymphocytes infiltrated between the fibers Throughout this area were patches of muscle fibers which were poorly stained and showed loss of their cross-striations Large numbers of small lymphocytes together with a few monocytes were present between the muscle fibers and surrounding the blood vessels. Within the myocardium of the right ventricle there were also found occasional polymorphonuclear leukocytes together with fibroblasts, proliferating capillaries and muscular debris Infiltrations of lymphocytes with a minimal degeneration of muscle fibers, accompanied by an increase of fibrous connective tissue, were found in the myocardium of the left ventricle in their second case.

In this connection, it may be appropriate to discuss myocardial changes that occur in cases of *scleroderma*, principally because of the relationship between dermatomyositis and diffuse scleroderma as discussed by Brock (1934). Weiss and associates (1943) reported in detail the postmortem findings in two patients with generalized scleroderma. These patients were part of a group of nine, all of whom had signs and symptoms of heart disease. The autho concluded that both the clinical and path logic studies indicated that the sclerode matous process is not confined to t skin but involves all organs. The ca diac failure is caused by myocardial sca ring of an unusual type. The scars we unusually vascular and it was thoug that they bore more resemblance to gran lation tissue *per se* than do scars resultin from arteriosclerosis or old myocardial i farction. No recent areas of infarction we encountered. No deposits of hemosider were present. One of the hearts containe many fibroblasts but only an occasion lymphocyte and mononuclear cell in a fe foci.

East and Oram (1947) also reported case of scleroderma. Scattered througho the myocardium were numerous areas o fibrosis. It is interesting that they coul not find cellular infiltrations in the hea except for small numbers of eosinophils i the fibrous tissue. Their patient also ha complete heart block and died from hea failure. They believed that, for some un known reason, the cardiac muscle fiber disappear in patches and are replaced b new connective tissue. They remarked tha their concept of the disease "might b summarized by the title of one of Strauss tone poems, *Death and Transfiguration.*

Myocarditis in instances of acute bac terial endocarditis and subacute bacteria endocarditis (Figure IX-55) (endocarditi lenta) has been discussed in connectio with the endocardial lesions.

Isolated Myocarditis. Allergic Myocarditi

Isolated myocarditis is one of the mos interesting types of myocarditis. It is o unknown origin, not accompanied by en docarditis or pericarditis, and occurs in pa tients who have no primary disease tha may be correlated with the myocarditis. It may be present in an apparently healthy person who, more or less suddenly, devel-



Figure IX-55 Myocarditis in endocarditis lenta Note perivascular infiltration of lymphocytes Hematoxylin and eosin X 200

ops progressive myocardial weakness and succumbs quickly. Clinically, the outstanding manifestations are progressive myocardial failure with a weak rapid pulse, low arterial pressure, and an increase in the area of cardiac dullness Electrocardiographic changes are often encountered but usually misinterpreted Precordial pain may be present The disease occurs at any age, although young people seem more frequently affected. Therefore, arteriosclerotic heart disease can easily be ruled out. There is no history of rheumatic fever The patients often die unexpectedly, as did 10 of 13 patients reported by Saphir (1942b)

Nomenclature. Earlier writers have used the terms "Fiedler's myocarditis," "interstitial," "circumscribed," "diffuse," "isolated," "idiopathic," "pernicious" and "granulomatous," singly or in combination, to describe the disease Although Fiedler (1899) termed this myocarditis "acute interstitial," it is clear from Fiedler's report that Schmorl, who studied the hearts of Fiedler's cases microscopically, described also parenchymatous changes in some of these with outspoken necrosis. The two cases reported by Ware and Chapman (1947) termed "chronic fibroblastic myocarditis," may also be classified as isolated myocarditis since they resemble those described by Boikan (1931) as pernicious myocarditis. However, these authors stated that it is possible that the etiology of this myocarditis may be traced to some acute or chronic infectious disease. Scott and Saphir (1929), who reported the first instances in the American literature, referred to "isolated myocarditis."

The literature on this subject has been reviewed previously Among more recent reports may be mentioned those of Covey (1942); Didion (1943), Marcuse (1947); Hertzog and Hayford (1947); and House (1948). Isolated myocarditis has often been reported in children (Bluhdorn, 1924, Kenny and Sanes, 1933, Maslow and Lederer, 1933, Lindberg, 1938; Smith and Stephens, 1938, and Greenebaum and associates, 1941; and others). Thus Saphir and co-workers (1944) referred to 41 such instances. It was reported in 8 children among the 36 patients of Marcuse's series, and House recently recorded its occurrence in 4 children. Jones and Marshall (1948) and Raeburn (1948) found this type of myocarditis in an eleven-month-old infant

Grossly, the hearts are usually enlarged and dilated Kiss (1947) emphasized the occurrence of hypertrophy in hearts having myocarditis. The myocardium is pale gray, often tinged faintly yellow with fine grayish or reddish streaks Histologically, the lesions are either diffuse or more circumscribed and principally interstitial in location, although the heart muscle fibers are also involved. In general, no characteristic cellular accumulations are present, nor does one particular type of cell predominate (Figure IX-56). Only Marcuse stated that he constantly found in his cases elongated cells with distorted nuclei, morphologically not identified with Aschoff cells or with Anitschkow myocytes Usually lymphocytes and endothelial leukocytes are the most commonly encountered cells. Polymorphonuclear leukocytes and eosinophilic leukocytes, however, are also present, and Saphir thought that mast cells, which are normally found within the inter-

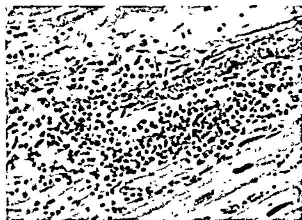


Figure IX-56 Isolated myocarditis Note that inflammatory cells are mainly lymphocytes and only a few are "cardiac histiocytes" Hematoxylin and eosin X 325

stitial tissue of the myocardium, seemed more numerous than normal. Transitions from the inflammatory cellular exudate to scar tissue are often found. House's first case disclosed widespread and diffuse absence of cardiac musculature with a moderate infiltration of polymorphonuclear leukocytes, lymphocytes, plasma cells, macrophages and large mononuclear cells The majority of the muscle fibers had been replaced by young granulomatous tissue. House suggested coronary occlusion as a possible factor, even though a careful examination did not reveal any such lesion. Because of the age of the patient (21 days), House also considered an infectious process developing *in utero*.

In other instances of isolated myocarditis, granulomas with giant cells are encountered This variety of isolated myocarditis has been termed *granulomatous myocarditis* (Figure IX-57) Neither tubercle bacilli nor spirochetes can be demonstrated in these hearts, although a history of either tuberculosis or syphilis may be obtained (Taussig and Oppenheimer, 1936). In such instances there usually are smaller or larger areas of necrosis at the periphery of which many lymphocytes, eosinophilic leukocytes and a few endothelial leukocytes are present, but there is no particular predominance of any of these types of cells. Likewise, the necrosis may be insignificant. The number of giant cells is conspicuous and their nuclei are arranged more or less toward the periphery. Some of these giant cells resemble those seen in tuberculosis, while many others are typical muscle giant cells. Numerous circumscribed areas contain no necrosis but consist of lymphocytes, eosinophilic leukocytes, and a few giant cells (Figures IX-58 and IX-59). These regions are richly vascularized, with thin-walled vessels. The adjacent myocardium discloses



Figure IX-57 Granulomatous (isolated) myocarditis Note presence of giant (muscle) cells Hematoxylin and eosin. X 150.

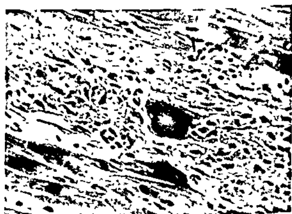


Figure IX-58 Granulomatous myocarditis. Note Ziehl-Neelsen stain did not disclose the presence of acid-fast organisms) Hematoxylin and eosin X 375.

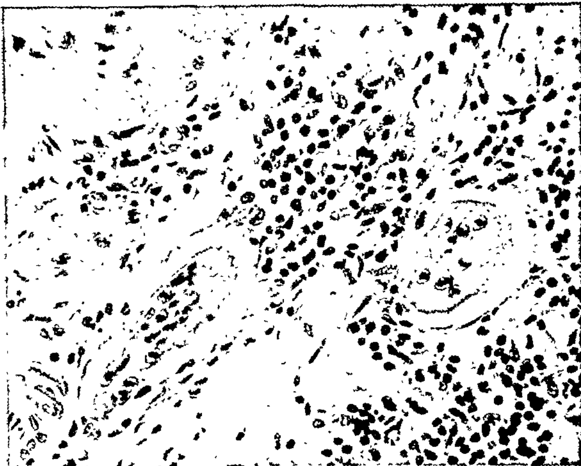


Figure IX-59 Giant cell granulomatous myocarditis X 150 (Courtesy, Armed Forces Institute of Pathology, Acc 85448)

a diffuse infiltration, predominantly of eosinophilic leukocytes and lymphocytes. Again, neither spirochetes nor tubercle bacilli are demonstrable

Earlier reports of this type of myocarditis were made by Baumgartner (1915), Saltykow (1905), and von Gierke (1921), and more recent relevant reports were given by Magner (1939); Sikl (1936, with review of the literature), Hansmann and Schenken (1938), Jonas (1939); Miller (1933), and Saphir (1942b) In discussing Miller's case, Lillie (1934) remarked that in experimental tularemia a granulomatous myocarditis is not infrequently found This is interesting because the question immediately arises whether or not there may be other infectious diseases that also produce granulomatous lesions in which the causative organism cannot be demonstrated and in which the granulation tissue is not characteristic enough to lead to the recognition of the etiologic agent Blastomycosis can be ruled out because blastomycetes are recognizable in sections. Sidorov (1935) reported a case of granulomatous myocarditis caused by *Balantidium coli* and actually demonstrated the organism

Trichinous myocarditis, however, is one form without a characteristic histologic picture Trichina larvae do not encyst in the myocardium (Gould, see page 842) Histologically, the myocardium in such instances shows focal or diffuse infiltrations of neutrophilic leukocytes, lymphocytes, and a

few mononuclear leukocytes and plasma cells. Usually many eosinophilic leukocytes are also present, although their absence is occasionally stressed. However, in isolated (Fiedler's) myocarditis also, a predominance of eosinophils may be rarely noted (Magner, 1939). The muscle fibers are degenerated or actually necrotic. The absence of the larvae, as stated above, does not preclude a diagnosis of trichinous myocarditis.

In a personal observation small, granulomatous lesions were found in the myocardium in a case in which *Trichinella spiralis* was encountered in the diaphragm. Histologically, the changes in the myocardium resembled those which are seen in granulomatous myocarditis and in diffuse isolated myocarditis. Only the discovery of trichinae in the diaphragm prevented us from classifying this as isolated myocarditis Weller and Shaw (1932) also noted the similarity of these two conditions, but Libman questioned the similarity of "eosinophilic" and isolated myocarditis, as reported by Smith and Stephens (1938). Thus, it seems clear that if attention is focused on the heart only, not only trichinous myocarditis, but perhaps also other types, *may well be confused with isolated myocarditis* On the other hand, the question must be raised if in some instances isolated, particularly granulomatous, myocarditis may not result from one of the known causes of inflammation.

It might be of interest in this connection to mention that a chronic type of myocarditis which very likely falls into the classification of isolated myocarditis was described in a young camel that died unexpectedly (Stunzi, 1947). The lesion consisted of scars with necrosis, many giant muscle cells, and foci of calcification.

Lindberg's report of isolated myocarditis is noteworthy because of his suggestion that the initial changes may be of the serous myocarditic type, similar to those found by Wenckebach (1934) in the beriberi heart, and described by Rossle (1934), and Eppinger and associates (1935). It is thought that the serous exudate of this type of myocarditis stimulates connective tissue overgrowth, and marked fibrosis ensues.

The myocarditis described by Lindberg (1938), and also by Boikan (1931), may perhaps have shown a "serous" component in its initial stage. More recently, Smith and Furth (1943) also remarked on the relation of isolated myocarditis to the beriberi heart Eppinger and associates also mentioned burns as possible causes of serous inflammation. Cases of isolated myocarditis are likewise reported in which burns are suggested as the possible etiologic agent (Zuppinger, 1901; Kaufmann 1922).

Because attempts have been made to identify isolated myocarditis as a type produced by chemicals, such as sulfa drugs, and also as the result of hypersensitivity, the myocarditis that occurs in these instances may be discussed here. Franz (1937) suggested that the myocardial lesions which he had observed may have been the result of the administration of *epinephrine*, or were possibly caused *by hypersensitivity* to epinephrine. Šikl, as early as 1936, asked if isolated myocarditis might not be classified as "idiosyncratic-allergic," rather than as "idiopathic" in the sense of unknown origin. He described 2 instances of myocarditis which followed treatment with *neosalvarsan*. Both of these patients had had syphilis. Both showed an acute eosinophilic myocarditis with granulomatous lesions, but neither tubercle bacilli nor spirochetes could be demonstrated. In reviewing the literature of so-called idiopathic myocarditis, he believed that there might be a few instances which were the result of hypersensitivity, particularly those having a history of urticaria or exanthematous skin lesion. French and Weller

(1942) described interstitial myocarditis, with many eosinophilic cells, in the hearts of 126 patients whose *sole* common factor was that one or more *sulfonamide drugs* had been administered shortly before death. Wells and Sax (1945) reported an instance of diffuse isolated myocarditis in which sulfadiazine was considered the possible etiologic agent. Microscopically there was a predominance of neutrophils in moderate numbers, occasional eosinophils and monocytic phagocytes and rare lymphocytes. French (1946) described histopathologic lesions in the myocardium *as the result of hypersensitivity to sulfonamide* chemotherapy The characteristic cell was the acidophilic histiocyte; also found were variable numbers of other mononuclear and polymorphonuclear cells, both acidophilic and neutrophilic These were either perivascular in distribution or diffusely distributed between the cardiac muscle fibers Necrosis was neither constant nor prominent, but did occur in the more severe cases Cellular infiltrates were present throughout the walls of capillaries and venules

Simon (1943) gave a summary of the pathologic lesions following the administration of sulfonamide drugs He also described those occurring in the heart Rich (1942) described an instance of recent periarteritis nodosa with a diffuse inflammatory cell infiltration of the myocardium composed of mononuclear and polymorphonuclear cells, including eosinophils. *Tissue from the scrotum*, removed 18 days before death and prior to administration of a sulfonamide, was examined on biopsy There had been *no evidence of* acute periarteritis within the scrotum at that time, but at autopsy numerous vascular lesions were found in the tissue immediately adjacent to the region of the scrotum from which tissue had been taken for biopsy. Because the periarteritis was obviously the result of the hypersensitivity to a sulfonamide, the myocarditis was also thus interpreted On the other hand, Fawcett (1948) attempted to determine if any fairly constant pathologic changes observed in the myocardium could be reasonably attributed to the use of the sulfonamide drugs He found that a comparison of the number of cases indexed as interstitial myocarditis in the necropsy files of the Mayo Clinic for two five-year periods, one prior to and one following the advent of sulfonamide therapy, revealed an identical number of cases in each group However, the possibility that the sulfonamide drugs may be responsible *for the production of an interstitial* myocarditis in an occasional instance was not denied Merkel and Crawford (1942) found no evidence of myocarditis in five patients whose death was attributed to sulfonamide drugs

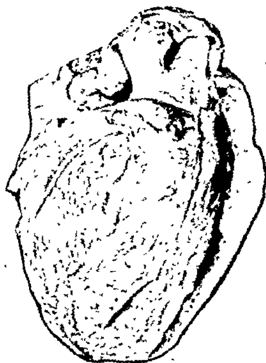


Figure IX-60 Polyarteritis nodosa Note nodules presenting on epicardial surface of heart (WCGH, 40 P 190) (Courtesy of Dr C H Binford)

The relationship of hypersensitivity and rheumatic carditis is discussed elsewhere.

It might be mentioned in this connection that Rich and Gregory (1943b) and a number of other investigators described in their experimental animals various myocardial lesions which were highly suggestive of specific lesions seen in the myocardium of patients with rheumatic fever. They emphasized that these lesions are the result of hypersensitive reactions of the anaphylactic type. While it is true that some of these myocardial lesions do resemble Aschoff bodies, myocardial changes described in isolated myocarditis in no way resemble those seen in rheumatic myocarditis; besides, acute panarteritis which also occurs as one manifestation of the anaphylactic type of hypersensitivity (Rich, 1942a; Rich and Gregory, 1943a), is not a feature of isolated myocarditis. It may be of interest in this connection to mention that von Albertini and Grumbach (1938) found experimentally that virulent organisms introduced into a partially immunized animal produced the same type of lesions as were roduced in the normal control animal with similar organisms of less virulence. For that reason they did not believe that allergy is of any significance in the etiology of endocarditis or myocarditis

In an experimental study, Gray (1949) found cardiac lesions of rheumatic type resembling those associated with experimental anaphylactic hypersensitivity in a high percentage of control Swiss mice. Treatment with multiple parenteral injections of egg white failed to influence the incidence and the severity of these lesions. Because of the recent interest in experimental myocardial lesions resembling myocarditis seen in rheumatic fever, it was emphasized that such lesions may be found in normal mice.

Jaffé (1946) stated repeatedly that chronic myocarditis in the sense of isolated or Fiedler's myocarditis is exceedingly frequently encountered in Venezuela. However, he believes that this myocarditis is the result of an allergic reaction towards *necrotic myocardial fibers*. Because the reaction of the interstitial tissues toward the muscle necrosis is always the same, even though various agents might have caused the original necrosis of the myocardial fibers, such types of myocarditis are morphologically identical. Thus Jaffé stated that isolated myocarditis may be caused by syphilis, bilharziasis, necator infestations and also beriberi and Chagas' disease. The original disease which had caused the myocardial necrosis may no longer be demonstrable but the myocardial lesions may remain (Jaffé).

Marcuse (1947) mentioned the following as possible causes of isolated myocarditis: bacterial infection, virus infection, sensitization to various substances, drugs causing increased heart action, dietary deficiency including general malnutrition, potassium deficiency, combined deficiency of potassium and vitamin B (see page 521). Virus infection as a cause was also suggested by Covey (1942), Schmidt (1948), and Finland and associates (1945).

In summary, there is a type of myocarditis of unknown origin which is not accompanied by endocarditis or pericarditis. It occurs in patients who have no other disease that may be correlated with the myocarditis. This myocarditis may also be present in apparently healthy persons who, more or less suddenly, develop progressive myocardial weakness and quickly succumb. Anatomically, isolated myocarditis does not vary in histologic detail from the myocarditis which is occasionally encountered in the course of acute infectious diseases. A diffuse and a granulomatous type can be distinguished. The latter is much rarer, and morphologically resembles somewhat the granulomas of tuberculosis and syphilis. Histologically, giant cells (muscle giant cells) are often recognized. Although nothing is known as to the cause

of either the diffuse or granulomatous form, it seems imperative in every instance to examine histologically other organs and structures besides the heart, in pursuit of the causative agent, as in trichinosis and tularemia. Recently, hypersensitivity to various chemical compounds, certain vitamin deficiencies, allergic reaction to either necrotic muscle fibers or some other agent, or a virus infection, have been regarded as responsible. However, it would seem wiser to classify myocarditis of known origin not as isolated myocarditis, but as "hyperergic," "chemical," etc. As more is learned concerning involvement of the myocardium under various conditions, the diagnosis of "isolated myocarditis" will become less frequent.

Myocardium in Tuberculosis

Horn and Saphir in 1935 reviewed the literature. Three main types can be distinguished, namely, the nodular, the miliary, and the diffuse infiltrative types. The latter should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis, or if the tubercle bacillus can be demonstrated either by guinea-pig inoculation, culture methods, or by staining methods Otherwise, this form of tuberculosis cannot be distinguished from the so-called specific productive myocarditis (Saltykow, 1914). For similar reasons it is difficult to attribute to a tuberculous origin, fibrous myocardial lesions which may be present in the hearts of persons dying of tuberculosis. Hence, the term "chronic interstitial tuberculous myocarditis" should be discarded.

Three instances of miliary tuberculosis of the myocardium were reported by Horn and Saphir (1935), in one of which a conglomerate tubercle also was present. These three instances occurred in children. The literature also discloses that the greater percentage of miliary tubercles in the myocardium occurred in children. This may indicate that the finding of miliary tubercles in the hearts of young persons dying of miliary tuberculosis is attended with less difficulty because of the relatively large areas examined histologically.

Among 97 children studied by Saphir and associates (1944), myocarditis was associated with tuberculosis four times. Actual tubercles were found in two infants. Both had diffuse miliary tuberculosis and one of them had tuberculous leptomeningitis. In two other children, two months and six years old, respectively, who also had diffuse miliary tuberculosis, the inflammation in the myocardium was diffuse and nonspecific. The myocardium of the two-month-old infant disclosed mainly an interstitial type of inflammation with many lymphocytes and a few endothelial leukocytes infiltrating the connective tissue septa. In the six-year-old child the involvement of the myocardium was rather localized, consisting of lymphocytes and endothelial leukocytes, and there was also some new formation of connective tissue. These lesions were found to be predominantly perivascular Tubercle bacilli could not be demonstrated in these hearts. This myocarditis cannot be classified as "tuberculous." The clinical findings in these two infants did not differ appreciably from those of the two previously mentioned children with tubercles *in the myocardium*, or from those of children who had the same type of generalized tuberculosis but no myocardial involvement

Albert (1938) found in a few hearts an "insignificant" number of lymphocytes and in one other, perivascular infiltrations of lymphocytes in addition to tubercles More recently attention has been paid to nonspecific myocarditis in tuberculosis and, in fact, there are workers who believe that sometimes such nonspecific inflammatory cells resemble those seen in Aschoff bodies (Masugi *et al.*, 1937). Roberts and Lisa (1943) discussed the relationship of these

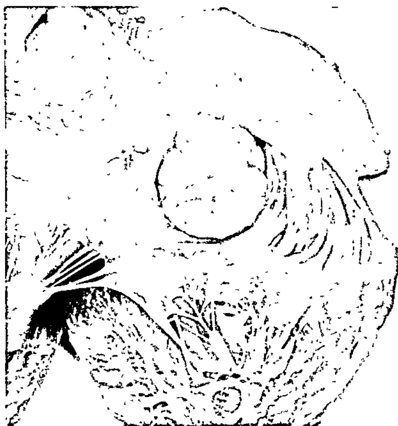


Figure IX-61 Tuberculoma of myocardium projecting into endocardium (Courtesy of Peder Lund, Medical Illustration Laboratory, Veterans Hospital, Hines, Illinois)

nonspecific inflammatory lesions to the lesions seen in rheumatic fever It must be realized, first, that it is always possible to encounter tubercles and Aschoff bodies in the same heart and, second, that simply because a lesion resembles an Aschoff body morphologically is no proof that the lesion in question signifies rheumatic fever. However, apparently because of this resemblance and because of the finding of tubercles and Aschoff bodies in the same heart, Masugi and his associates suggested that rheumatic fever might be of tuberculous origin.

Amersbach and associates (1931) reported the presence of tubercle bacilli in tonsillar tissues in patients with recurrent rheumatic arthritis. It seems probable that these authors were dealing with patients who had both diseases.

It has also been suggested that morphologically nonspecific inflammation in the myocardium in tuberculosis may be the result of a secondary nontuberculous infection This seems more logical because one occasionally finds myocarditis associated with other pulmonary lesions, such as bronchopneumonia and bronchiectasis.

An unusual myocardial involvement was described by Jones and Tilden (1942). An 11-year-old girl with tuberculous cervical lymphadenitis died unexpectedly. The autopsy disclosed conglomerate tuberculosis of the myocardium, which had caused a tuberculous (mycotic) aneurysm at the base of the left ventricle. The unexpected death resulted from rupture of the aneurysm and consequent hemopericardium. Tuberculous myocarditis with endocardial thrombosis and subsequent embolism from these thrombi has also been reported by Beebe and Coleman (1945). The nodular variety of tuberculosis (tuberculoma) is the most frequent form (Figure IX-61).

Rauchwerger and Rogers (1947) who reported such an instance, stated that this form usually occurs as yellowish gray, rounded, fairly firm nodules which may vary in size from less than a centimeter to that of an egg. They may be well defined or may merge with the surrounding parenchyma. The common site is the wall of the right atrium. Their ability to produce symptoms, of course, depends upon their size and location. With a few notable exceptions, most of the reported cases have been without subjective or objective signs of cardiac involvement. Rosenbaum and Linn (1948) agreed with the common concept that the wall of the right atrium is the most common site of nodular tuberculosis They also reported an instance of tuberculoma of the interatrial septum of the heart.

In a patient with paroxysmal ventricular tachycardia Schnitzer (1947) found at autopsy miliary tuberculosis of the myocardium involving the interventricular septum.

Boeck's Sarcoid

There are cases on record of involvement of the myocardium in Boeck's sarcoid. Saphir (1942a) has referred to the older literature Johnson and Jason (1944) thought that perhaps some of the cases reported as "granulomatous myocarditis" (isolated myocarditis, see above) might have been examples of sarcoidosis of the myocardium.

Scotti and McKeown (1948) referred to 12 such instances reported in the literature, and reported a case of their own The epicardium or pericardium was involved three times, the myocardium alone three times and the pericardium and myocardium seven times Three of these 13 patients had died unexpectedly. Grossly, the myocardium was dark brown and firm and showed no abnormalities. Microscopically, nodules composed of epithelioid cells, lymphocytes, and occasional giant cells were found in the subepicardial fat One of these nodules was adjacent to a coronary artery but did not involve its wall. Multiple granulomas were present in sections of the myocardium of the left atrium, in the interventricular septum, and in the papillary muscles and the wall of the left ventricle In some cases, small collections of lymphocytes without other cellular components were also seen in the myocardium Granulomatous lesions were also noted in lymph nodes, lungs, liver and the prostate gland Unexpected death was attributed to the active lesions and to prominent fibrosis extensively involving the myocardium Ricker and Clark (1949) in a recent review of sarcoidosis found the heart involved only twice among 195 cases.

Myocardium in Syphilis

It is still controversial whether or not syphilis may involve the myocardium in the form of a nonspecific subacute or chronic inflammation. Excluding congenital syphilis of the heart, gummas in the myocardium or gummatous myocarditis (microscopic gummas), the controversy centers about the possible occurrence of a diffuse myocarditis that may be brought about by the presence of the *Treponema pallidum*. In 1932 Saphir reviewed the literature pertaining to so-called chronic syphilitic myocarditis and listed the characteristics of syphilitic myocarditis as recorded in the literature A critical consideration revealed that, morphologically, this diagnosis could not be made in any of the reviewed cases in the absence of gummas. He summarized the findings in 130 hearts which had associated syphilitic aortitis and insufficiency of the aortic valve The myocardium in these 130 hearts showed no changes which from a morphologic point of view could be interpreted as syphilitic myocarditis. All the changes observed might be encountered in other conditions.

In this study the findings of Warthin, who believed that syphilitic myocarditis is a frequent finding, were analyzed. Attempts were made to duplicate Warthin's (1918) demonstration of spirochetes.* Using the autopsy material at the Michael Reese Hospital and employing first Warthin's staining technic and later a special technic devised in the laboratory of this hospital (Garvin, 1938), a diligent search proved futile, in none of these hearts were spirochetes found. Gore (1947) remarked that Warthin's assertion that myocarditis is frequent in this disease has acquired a tenacious hold, with the result that physicians are prone to make a diagnosis of syphilitic myocarditis. He concluded that there is an abundance of irrefutable evidence that, except for a rare gumma, myocardial changes in cardiovascular syphilis can be attributed almost entirely to vascular changes: narrowing of the coronary ostia or arteriosclerosis. Gore (1947) confirmed these observations in a review of material available at the Armed Forces Institute of Pathology.

As far as the patient with syphilitic heart disease is concerned, it cannot be overemphasized that in every case, sooner or later, the heart will be fatally damaged (Norris, 1937). From the point of view of the clinician, it does not make much difference whether the myocardial damage is the result of primary changes at the mouths of the coronary arteries resulting from syphilitic aortitis, or is caused by primary inflammatory changes in the myocardium itself. However, it seems clear, from numerous reports and from clinical observations in general, that when the blood supply of the heart is interfered with, particularly if the interference is at the orifices of the coronary arteries, the resulting condition is more serious than that which is due to an inflammatory process in various foci within the heart muscle, provided that the inflammation does not involve the conduction system. The saying of the older clinicians, that the first failure of a syphilitic heart is usually the last, well illustrates this fact.

Norris, reviewing some of the literature and alluding to the controversy on the demonstration of spirochetes, stated that while he was not able to find the spirochetes with Warthin's facility, he believed that years of experience taught Warthin more about heart-forms of spirochetes than was known by any other living pathologist. Norris also pointed out that spirochetes also elongate, separate and fragment in syphilitic lesions, and at times may be obscured by their twists, spirals and dissimilar appearances as compared to spirochetes in fetal or acute syphilitic ulcerations; that as the syphilis grows older the spirochetes become hidden, quiescent and inactive; and that treatment also tends to obscure them.

Weller and Shaw (1932), in a study on trichinosis, also referred to the difficulties in the demonstration of spirochetes in the myocardium, even in cases of clearly demonstrable syphilitic myocarditis or when the aortas of the same patients showed countless numbers of easily stained organisms. One must believe, they emphasized, that these observations have a broad biologic significance in that they point to a special evolutionary endowment of the heart muscle with antiparasitic powers not possessed by most of the other tissues of the body. Magill (1935) presented five patients, all Negro males, with positive Wassermann tests and unexplained cardiac failure. Although the Levaditi and Warthin staining methods did not reveal the Treponema in the myocardium in any of these cases, microscopically the myocardium in every instance showed marked infiltration of round cells with associated fibrosis between the muscle bundles and

* For some of the references to Warthin's extensive studies, see Saphir (1932).

around the smaller blood vessels. He considered the evidence circumstantial in favor of a syphilitic origin for the myocarditis.

It must be pointed out, as demonstrated in Saphir's review (1932), that the infiltration by round cells, even in a perivascular location, and the scarred areas occur in various types of myocarditis and morphologically are not of themselves pathognomonic of syphilis. That myocardial inflammatory changes may occur in syphilitic patients just as in other patients is clear, but the fact that they do occur in syphilitic patients does not denote a syphilitic origin for these changes.

Šikl (1936) stated that, in a patient showing symptoms of myocarditis and having a positive Wassermann reaction, myocarditis may or may not be syphilitic, since it may represent a mere coincidence of some nonspecific process in a patient with venereal infection. Even the apparent effectiveness of antisyphilitic therapy may be misleading.

Reifenstein (1936) reported an instance of acute myocarditis simulating acute myocardial infarction. He pointed out that pathologists have been unable to distinguish the fibrous changes found in the myocardium in known syphilis from the fibrous changes found in other conditions, including arteriosclerosis. This deficiency as well as the failure to find spirochetes in the myocardium has been used as evidence against Warthin's concept that a specific form of myocarditis is found in syphilis Reifenstein felt that it was unfortunate that the discussion on syphilis of the myocardium had centered around the question of occurrence of a specific form of myocarditis other than the gummatous type. He stated that there is no question that gummas may occur in the myocardium just as in other organs or structures The occurrence of gummatous myocarditis is accepted generally; the only question is whether there is an acquired syphilitic type of myocarditis, more or less diffuse, showing nothing characteristic of syphilis in the absence of demonstrable spirochetes in the myocardium.

From the foregoing it is clear that a number of changes are found in the myocardium in instances of syphilitic aortitis, particularly in those also showing aortic insufficiency and narrowing of the mouths of the coronary arteries. It is also clear that a number of patients who have syphilitic heart disease have acute infectious diseases which *per se* may cause a nonspecific type of myocarditis.

Clawson (1941) examined microscopically five blocks from each of 105 hearts with syphilitic aortitis. A few small fibrotic areas of the type commonly seen in hearts with coronary sclerosis were encountered. Also small proliferative inflammatory areas were noted in a few hearts and an occasional patch of lymphocytic infiltration was present in a relatively small number, but syphilitic myocarditis was not mentioned Blocks from 71 hearts were stained by the Levaditi method and examined for spirochetes, but none were found

Norris (1939) found gray or pale white fairly well defined spots within the left heart wall, surrounded by zones of hyperemia which he considered to be characteristic of syphilitic myocarditis. Histologically he encountered infiltrations of lymphocytic cells, fibroblasts with an occasional giant cell and many plasma cells. There also were many new thin-walled blood vessels, a number of which were surrounded by lymphocytes.

Mention must also be made of the so-called "critical" (malignant) syphilitic myocarditis of Warthin (1925) Corrigan (1941) studied this subject and reviewed the pertinent literature. She reported myocardial infarcts in five hearts in syphilitic aortitis. In two the infarcts were the result of syphilitic changes in the aorta and at

the mouths of the coronary arteries, and in three they were caused by concomitant coronary arteriosclerosis and thrombosis. She stressed the histologic similarity between very recent infarcts (as indicated by the presence of polymorphonuclear leukocytes) and the "malignant syphilitic myocarditis" of Warthin.

Jaffé (1946) stated that there is a kind of diffuse "syphilitic" myocarditis which is not produced by spirochetes but by a local allergic reaction, as has been mentioned previously. He stated that the diagnosis can be made only in the presence of other syphilitic lesions in the body. Interestingly enough, he emphasized that this kind of myocarditis is rarely observed in Europe and in the United States, but is frequent in Venezuela He recognized three kinds of myocardial syphilis (1) diffuse myocarditis, (2) gummatous myocarditis (microscopic gummas), and (3) gross cardiac gummas

Gummas in the myocardium are rarely reported. Saphir (1932) reviewed the literature for their incidence. Clawson in 1941 found only five instances of gummas in the myocardium in 30,265 autopsies. Spain and Johannsen (1942) reported 3 cases of localized gummatous myocarditis. In one case the gumma had impinged on both the tricuspid and pulmonary valves, and in another case the gumma had invaded the posterior leaflet of the mitral valve Kobernick (1947) reported an instance of gumma of the coronary artery and a gumma of the heart. He stated that only 100 cases of gummas had been reported in the literature.

From the available literature and from personal studies it must be concluded that the entity "syphilitic myocarditis," a diffuse syphilitic inflammation with the presence of spirochetes, in acquired syphilis, is extremely rare, if it occurs at all. This does not mean that the final word has been spoken, but it should be a stimulus for further exhaustive studies closely linked with the problem of syphilis in general. The hearts of syphilitic patients should be subjected to a careful search for microscopic lesions. Every method available for demonstrating spirochetes should be used. More thorough studies of the cultural characteristics of *Treponema pallidum* and animal experiments are essential, always having in mind the possibility of producing specific myocardial changes and taking into consideration the immunologic state of the host. Perhaps, after a more concerted effort, more will become known concerning syphilitic myocarditis.

Weil's Disease (Infectious Spirochetal Jaundice). Mollaret and Ferroir (1935) reported an instance of fatal myocarditis in Weil's disease They found swelling of the heart muscle nuclei and chromatolysis. The interstitial tissue was infiltrated by lymphocytes and polymorphonuclear leukocytes. In one region a necrotic focus was demonstrated. They particularly emphasized the extreme dilatation of the capillaries. Leptospirae were not found in the myocardium.

Myocarditis in Virus Diseases

During the past twenty years occasional reports have appeared in the literature of myocardial changes in diseases now recognized as of viral origin. More recently experimental work with various viruses, identification of certain viruses in patients who subsequently died with myocarditis, and electrocardiographic changes in patients with well-known virus disease have shown conclusively that myocarditis occurs in virus diseases.

Helwig and Schmidt (1945) isolated a virus from a group of anthropoid apes dying from interstitial myocarditis, and were able to produce myocardial lesions consistently in mice. Schmidt (1948) reported the isolation of an agent from a chimpanzee dying of interstitial myocar-

ditis, which produced myocarditis and encephalitis in mice and hamsters and myocarditis in guinea pigs (virus of "encephalo-myocarditis"). He remarked that the morphologic findings in the heart duplicated, to a remarkable degree, the myocardial lesions found in human heart muscle in several virus diseases. He also suggested that isolated myocarditis of man (Fiedler's myocarditis) might be caused by a virus

Warren (1948) found, in serums from 17 patients with so-called three-day fever which occurred among Army personnel stationed in and near Manila, appreciable amounts of specific neutralizing antibodies for the virus of encephalo-myocarditis In this connection, the work of Pearce and Lange (1947) may be mentioned here They found that the incidence and severity of myocarditis, in rabbits suffering from a variety of viral infections, are markedly increased when these animals are subjected to procedures that tend to decrease the amount of oxygen supplied to the heart

Lyon (1947) emphasized that from a clinical point of view, importance should be attached to virus myocarditis connected with epidemic infective hepatitis, infectious mononucleosis, yellow fever, varicella, dengue, poliomyelitis, atypical primary pneumonia, rubeola, measles, mumps and influenza-like infections Because of the benign character of the majority of these diseases, myocardial involvement is usually overlooked. Ungar (1948) described "nonpurulent myocarditis" in acute *epidemic encephalitis*, the myocardium containing infiltrations mainly of lymphocytes and of relatively few polymorphonuclear leukocytes.

Poliomyelitis. Myocarditis is frequent in poliomyelitis. Saphir (1945b) found myocarditis in 10 of 17 patients who died of poliomyelitis. Histologically, the inflammatory cells consisted principally of lymphocytes and neutrophils, occasionally diffuse infiltrations of polymorphonuclear leukocytes were noted In patients dying within the first week of the infection, the myocardium showed many neutrophilic polymorphonuclear leukocytes (Figure IX-62), sometimes massively invading the myocardium. Later more and more mononuclear cells appeared (*Figure* IX-63). In patients dying four to six weeks after the onset of symptoms of poliomyelitis, the myocardium contained many lymphocytes and monocytes, principally in the interstitial tissue Among 35 autopsies of victims of poliomyelitis Ludden and Edwards (1949) found myocarditis in 14. They pointed out that proof that the cardiovascular lesions in acute poliomyelitis are caused by the virus of poliomyelitis will depend on the demonstration of the virus in the lesions and on the experimental production of such lesions. (See also Saphir and Wile, 1942.) Ludden and Edwards observed lesions similar to those which have been described in other infectious diseases and in Fiedler's myocarditis. They asserted that myocarditis should be suspected in every patient who is seriously ill with acute poliomyelitis It is interesting to note that in one of their cases there was rupture of the right atrium, with resulting hemopericardium Histologic study showed degenerative myocardial changes. The mus-

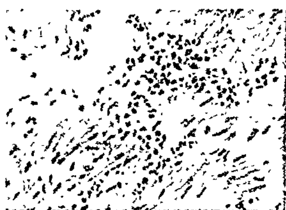


Figure IX-62. Myocarditis associated with poliomyelitis Patient died 12 hours after onset of symptoms Note almost exclusive presence of polymorphonuclear leukocytes Iron-hematoxylin X 300.

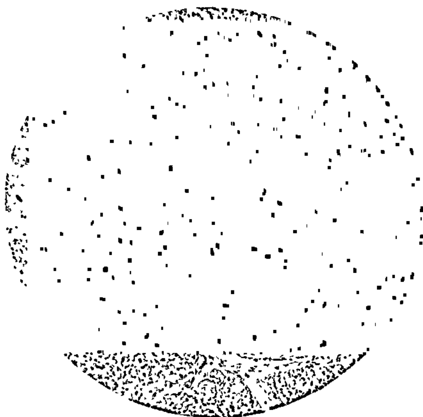


Figure IX-63. Myocarditis in poliomyelitis The patient died late in the course of the disease. Hematoxylin and eosin. X 100 (WCGH, 45 P 191 M.)

cle fibers, particularly near the area of the perforation, showed loss of striation and few neutrophils. Dolgopol and Cragan (1948) found focal myocarditis in 16 of 92 cases of poliomyelitis. The incidence of myocarditis in 45 cases, in which multiple sections from each heart were available, was 26.6 per cent They thought that cardiac failure was the immediate cause of death in at least 4 patients. From the evidence at hand, it seemed probable that these lesions were produced by the virus which caused poliomyelitis. Whether or not this assumption is accurate, it is apparent *that myocarditis occurs frequently in* poliomyelitis. Spain and associates (1950) found myocarditis in 12 of 14 patients with poliomyelitis. It is noteworthy that in one of these the myocarditis was diagnosed clinically. They believed that the myocarditis was caused by a virus.

Jungeblut and Edwards (1951) isolated the virus of poliomyelitis from the heart of two patients with poliomyelitis, thus proving that the myocarditis was actually caused by a virus.

Influenza. Nonbacterial myocarditis was also reported in influenza A infection in which the virus had been isolated from the lungs. Cardiac disturbances, such as bradycardia, extrasystoles, partial or complete heart block, sino-nodal block, loss of various complexes and T wave changes in the electrocardiogram, which may be observed after influenza, may be explained on the basis of myocarditis. Finland and associates *(1945) reported 2 such instances* in which they found necrosis of muscle fibers with extensive infiltration of lymphocytes, plasma cells, large mononuclear cells, and occasional eosinophils and mast cells. They emphasized that a prolonged and diligent search had been made for evidence of myocardial damage. Inflam-

matory changes in the myocardium have also been reported by Binford and Hauser (1944) in severe pneumonitis, in which *minute coccobacillary inclusions* were encountered in a few alveolar lining cells, in a few cells of the alveolar exudate, and in one Kupffer cell in the liver. Microscopic examination of the myocardium disclosed a few clusters of mononuclear cells distributed around interstitial capillaries and larger vessels.

Infectious Mononucleosis. Lyon (1946) reported acute myocarditis with electrocardiographic changes in the terminal deflections of the chest lead, as a sequel of infectious mononucleosis. A detailed study by Custer and Smith (1948) disclosed changes in the myocardium in 6 of 8 autopsies of patients with infectious mononucleosis. Aggregates of lymphocytes were sparsely distributed within the myocardium about small blood vessels. They were also present in small numbers beneath the endocardium. In only one case was the reaction virtually negligible. In another, the cellular infiltrate was rather prominent. Allen and Kellner (1947) emphasized the finding of a few interstitial collections of mononuclear cells and lymphocytes of moderate size in these instances.

Rubeola (Measles). Degen (1937), in a study of 100 fatal cases of measles found pericarditis in 4. In 2 there was a shaggy exudate on the visceral pericardium, and the pericardial sac was distended with purulent fluid, while in 2 there were lesser amounts of purulent fluid and no fibrinous exudate. *Pericardial effusion* was somewhat more common, effusion of clear fluid being noted 23 times. The heart itself showed no characteristic gross changes. Dilatation of the right side of the heart was found 24 times. Of 91 hearts examined microscopically, only 4 showed more than the usual toxic changes. These 4, including the 2 with exudative pericarditis, had cellular infiltration in the myocardium. The infiltration was chiefly lymphocytic and was partially, but not predominantly, perivascular. Warthin (1931) described as the essential lesion of the prodromal stage of measles a subepithelial infiltration of multinucleated syncytial giant cells, lymphocytes and monocytes in the tonsils and pharyngeal mucosa. Since this discovery there have been several reports of autopsy findings in measles, notably those by Minami (1938) and by Semsroth (1939). Neither of these investigators mentioned any changes in the myocardium. From the scarcity of pertinent literature it must be concluded not only that true myocarditis is rare in measles but also that cardiac complications are rarely encountered clinically. Complete heart block occurring during the pre-eruptive stage of *rubella* (German measles) was reported by Logue and Hanson (1945).

Epidemic Parotitis (Mumps). Recently electrocardiographic evidence of myocardial involvement in mumps has been reported.

Wendkos and Noll (1944) claimed to have described the first known case of myocarditis complicating mumps in which the diagnosis was established during life. Rosenberg (1945) observed complete heart block in 2 patients with epidemic parotitis. Among 104 consecutive patients with epidemic parotitis, evidence of myocardial involvement was observed 16 times (15.4 per cent). In all but 2 patients, the electrocardiographic changes were transitory. Felknor and Pullen (1946) reported a clinical instance of myocarditis complicating mumps, in which both clinical and electrocardiographic confirmation of the diagnosis could be made. No etiologic cause for the myocarditis other than mumps could be determined. In an analysis of a four-year epidemic of mumps, Eagles (1947) encountered questionable myocarditis 3 times among 1664 cases reviewed.

Manca (1932) reported a singular instance of myocarditis with mumps The patient was a 21-year-old soldier who contracted the disease during a severe epidemic in the barracks and died rather unexpectedly. The myocardium grossly was yellowish pink and opaque and was likened to boiled meat. Histologically, a serous and cellular exudate was seen, consisting of polymorphonuclear leukocytes, some lymphocytes, plasma cells and young fibroblasts. In addition, large cells were present with much cytoplasm and round nuclei, the chromatin of which formed a coarse network, there was also cloudy swelling of the muscle fibers Bacteria were not seen in the section.

It is interesting to note that as early as 1918 Pujol had observed clinical evidence of myocarditis in patients with mumps. At that time he pointed out the absence of histologic studies of hearts in mumps.

In *yellow fever* myocardial degeneration is frequent but evidence of inflammatory changes is found only occasionally (Adler and Lyon, 1947). In experimentally produced yellow fever, outspoken myocarditis has been observed by Lloyd (1931) and by others. Wood (1946) found myocarditis in an instance of early acute *hepatitis* complicated by spontaneous rupture of the spleen and fatal hemoperitoneum Small groups of lymphocytes with occasional mononuclear phagocytes infiltrated the myocardium between the muscle fibers of the trabeculae carneae and also were prominent immediately beneath the endocardium Electrocardiographic changes with infectious hepatitis were also reported by Dehn and associates (1946).

There are no recent reports available in regard to myocarditis in *varicella* (chicken pox) and in *variola* (smallpox). Only the classical description by Councilman and associates (1904) of the anatomy and histology of variola may be quoted. In 4 cases, they found microscopically an interstitial cellular infiltration of large basophilic cells. In one instance there was a general infiltration beneath the entire endocardium, but small foci of inflammatory cells were found elsewhere.

Myocardial changes have also been described in instances of *hoof-and-mouth-disease* in cattle by Holz (1943).

Though *Friedreich's ataxia* is not considered a virus disease, it may be mentioned that Russell (1946) reported 4 cases in which Friedreich's ataxia was associated with a chronic interstitial myocarditis, 3 of the 4 patients having pronounced cardiac hypertrophy. Examination of the medulla oblongata failed to reveal any histologic abnormality in the region of the vagal nuclei. Russell argued that the myocarditis is of toxic origin, and in view of the known association between the nervous and cardiac disorders in Friedreich's ataxia, it is probable that the same agent is responsible for both lesions Hejtmancik and co-workers (1949) reported changes in the electrocardiograms of 2 patients with Friedreich's ataxia Autopsy performed on one of these disclosed diffuse myocarditis with fibrosis. There were no specific changes.

Myocarditis has also been reported in the *Landry-Guillain-Barré* syndrome, a disease entity of unknown but perhaps of viral origin. In autopsies of 50 such cases, Haymaker and Kernohan (1949) found 7 instances in which a mild focal myocarditis was observed, consisting of perivascular accumulations of lymphocytes, macrophages and Anitschkow cells.

A number of investigators have concluded that the myocardial lesions are due to the actual presence of the virus. However, others maintain that it is difficult to assay the importance of the viral disease as the cause of myocarditis since bacterial infections are often found in fatal cases. Inasmuch as it has been shown experimentally that reduction of the oxygen supply to the heart markedly increases the

severity of virus-induced myocarditis, it may well be that a complicating pneumonia, by decreasing the oxygen supply to the heart, serves to intensify the virus myocarditis in such patients.

Myocarditis in Rickettsial Diseases

Typhus. Wolbach and associates (1922) in their extensive monograph described inflammatory changes in the myocardium in instances of typhus The characteristic lesions were nodular, were present most often in the inner half of the ventricular wall and consisted of collections of cells in which large ameboid and phagocytic mononuclears (endothelial cells) predominated, lymphoid and plasma cells were numerous and mast cells and eosinophils were fairly common Polymorphonuclear leukocytes were present in small numbers; they were more numerous when there was necrosis of muscle fibers. The necrosis usually involved only a portion of one or several muscle fibers. It was often impossible to recognize the obliterated blood vessels in these focal lesions. Capillaries filled with endothelial cells and frequently with fibrin thrombi were found in early lesions A more diffuse infiltration of the myocardium was invariably composed of endothelial cells, lymphoid cells and plasma cells, which lay packed between capillaries and (apparently) normal muscle fibers. In 97 per cent of 103 cases of typhus examined by Herzog and Rodriguez (1936), myocarditis was found which was described as "myocarditis exanthematica" This was characterized by submiliary perivascular nodules, consisting principally of adventitial cells, fibroblasts, lymphocytes, polymorphonuclear leukocytes and plasma cells. Often the polymorphonuclear leukocytes predominated.

Settle and associates (1945) reported autopsy findings of 55 patients with *scrub typhus* (tsutsugamushi disease) occurring in American troops in British and Dutch New Guinea and adjacent islands. Grossly the heart exhibited relatively mild changes and contained minute, focal, pale, brownish gray areas of degeneration or, more rarely, small recent focal hemorrhages Microscopically, the dominant lesion in all cases was acute nonsuppurative myocarditis, focal as well as diffuse, which varied in severity. It was characterized by perivascular infiltration of mononuclear cells, plasma cells, occasional lymphocytes and polymorphonuclear leukocytes. Sometimes large multinucleated cells with vesicular nuclei and basophilic cytoplasm were encountered Frequently the vascular endothelium was swollen or thickened by proliferating lining cells, recent mural thrombi overlapping the endothelium Allen and Spitz (1945) reported a comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases Table IX-17, taken from their study, shows the comparative degree of interstitial myocarditis in scrub typhus, epidemic typhus and Rocky

TABLE IX-17

Comparative Degree of Interstitial Myocarditis
in Scrub Typhus, Epidemic Typhus and Rocky Mountain Spotted Fever
(From Allen and Spitz, 1945)

Disease	Degree of Interstitial Myocarditis										Total No. of Cases
	0		+		++		+++		++++		
	No of Cases	%	No of Cases	%	No. of Cases	%	No of Cases	%	No of Cases	%	
Scrub typhus	5	7	32	44	27	35	8	11	2	3	74
Epidemic typhus	4	17	12	50	5	21	3	12	0	0	24
Rocky Mountain spotted fever	2	17	7	48	3	25	0	0	0	0	12

Mountain spotted fever. From this table it appears that myocarditis is often encountered in these rickettsial diseases. Seemingly, it occurs more often and to a more severe degree in instances of scrub typhus. They found no evidence that the right side of the heart was involved more frequently than the left side, that the ventricles were more severely damaged than the atria, or that one part of the wall of the ventricle was selectively involved, as has been stated by previous investigators. However, they emphasized the uneven distribution of myocarditis and that in some sections the plasma cell may be the predominating cell, in others the acidophilic macrophage, and in still others from the same case, the Anitschkow myocyte. Giant cells were also present.

Polymorphonuclear leukocytes were prone to occur more often in *Rocky Mountain spotted fever.* The infiltrations were located principally between the muscle fibers, although they were also found in the periarterial fibrous tissue and rarely within the sarcoplasm of muscle fibers. Only exceptionally was there found an isolated, swollen, partially hyalinized fiber, in the sarcoplasm of which there were one or two karyorrhectic inflammatory cells. The myocardial fibers were usually well preserved. In scrub typhus obvious fibrinoid degeneration of arteries of the heart was not found, but such a change was occasionally encountered in the other types of typhus. Necrotizing arteritis, however, was seen in 4 (17 per cent) of the cases of epidemic typhus. Involvement of the mural endocardium by mononuclear infiltrates was often striking in scrub typhus.

In a postmortem study of 31 cases of scrub typhus, Levine (1946) found the *principal cardiac changes to be in the myocardium.* It is interesting that he described necrosis of the heart muscle fibers in about one-half of the cases showing carditis. However, he emphasized that necrosis was rarely severe. The essential pathologic response to the infection consisted of endothelial proliferation and infiltration with perivascular lymphocytes, plasma cells and many mononuclear cells

Schopper (1943), who studied the material obtained by the Germans during World War II, also described extensive interstitial myocarditis in typhus. Among 70 cases of typhus, myocarditis was severe in 19, moderate in 14, and slight, principally interstitial, in 19, myocarditis was not found in the remaining 18.

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CHAPTER X

Parasitic Diseases of the Heart

WALTER A STRYKER

LESIONS OF THE HEART resulting from parasitic (protozoal and helminthic) infection may be specific, by virtue of the presence of the parasitic agent within the tissues of the heart or pericardium, or nonspecific, the changes being secondary to the presence of the parasite in an adjacent or distant site. In some parasitic diseases cardiac lesions are a major feature, and upon their extent may depend the seriousness of the infection. In many types of human parasitic infection, no cardiac lesion has been reported.

Protozoal Infections

Amebiasis. Amebic involvement of the heart is a rare complication of amebiasis. At least 44 proved cases have been reported in the literature (Carter and Korones, 1950); in every instance, the lesion was an amebic pericarditis. Usually it was secondary to amebic disease of the liver (Kern, 1945). In numerous other cases (Edwards, 1947) there have been cardiac symptoms or findings in patients with intestinal amebiasis or amebic hepatic or pulmonary abscess, but definite proof of the amebic nature of the cardiac lesion was lacking. In one of the earliest reports of amebic pericarditis by Howard and Hoover (1897), an amebic (tropical) abscess of the liver was further complicated by a fibrinopurulent pericardial exudate in which amebae were found. There was no actual rupture of the hepatic abscess into the pericardium. Craig (1904) reported two cases of "acute pericarditis, due to perforation of an amebic abscess of the liver into the pericardial cavity." In Clark's review (1925) of postmortem examinations of 186 patients with amebiasis, no instances of amebic cardiac involvement were found. Ochsner and De Bakey (1943) found one example of amebic pericarditis among 181 patients with amebic hepatitis and amebic hepatic abscess. They stated that less than 2 per cent of subjects with amebic involvement of the liver have cardiac complications. They believe that such complications are more likely to follow amebic abscesses of the left lobe of the liver, since abscesses in this lobe of the liver are more difficult to diagnose.

Grossly the parietal pericardium is thick-

ened up to 5 mm. or more The pericardial cavity contains a thick greenish yellow purulent material which is usually adherent to both pericardial surfaces. The surfaces are yellow-gray and granular. The usual landmarks are obscured On microscopic examination both the parietal and visceral pericardial surfaces consist of a thick fibrous connective tissue with surfaces covered by necrotic material This material is backed by granulation tissue with numerous large mononuclear cells, occasional lymphoid and plasma cells, and sometimes also a few polymorphonuclear leukocytes Individual or small clusters of amebae may be found in the necrotic tissue and also in the deeper layers of the pericardium Typical is the small halo of cytolysis surrounding each ameba; phagocytosed red blood cells may be found within the parasite The myocardium usually shows no change (Kern). It is not unusual to fail to find amebae in the fluid removed from a lesion which subsequently proves to be amebic in origin Ochsner and De Bakey found amebae in only 16.5 per cent of cases in which the contents of hepatic abscesses were studied The parasites may remain within the wall of the cavity (See Figure X-1)



Figure X-1 Trophozoite of *Endameba histolytica* (surrounded by inflammatory cells) in pericardial fluid Paraffin-block section. Iron-hematoxylin stain X 2400 (*From M G Carter and S. B Korones, New England J Med*, *242* 391, *1950* Courtesy of the authors and the editor)

In many amebic infections, especially of the liver, in which there is no specific involvement of the pericardial cavity, the heart will show nonspecific changes, such as fatty degeneration and cloudy swelling.

Trypanosomiasis. Human trypanosomal infections are characterized by the development of two quite different diseases. African sleeping sickness is the result of infection by either *Trypanosoma gambiense* or *Trypanosoma rhodesiense*. South American trypanosomiasis, also known as Chagas' disease, is caused by *T. cruzi*. Cardiac lesions occur in both diseases, in sleeping sickness the major lesions are cerebral and the cardiac lesions largely represent a complication, while in Chagas' disease the myocarditis is as important as the cerebral lesions, and may be most important as a cause of chronic cardiac disease.

Cardiac lesions are found in infections caused both by *T gambiense* and *T rhodesiense*. As is true of the cerebral lesion, the changes in the heart are more acute and severe in the rhodesiense form (Hawking and Greenfield, 1941) The heart is of normal size but is pale and flabby. Microscopically, inflammatory infiltrates are seen around the smaller blood vessels in the endocardium, myocardium and pericardium (Thomas and Breinl, 1905). The left ventricle is affected more frequently than is the right. The cells are chiefly lymphocytes and plasma cells, although eosinophils, mast cells and giant cells have also been described Muscle fibers adjacent to the inflammatory foci frequently show loss of striations or fragmentation. (For discussion of Fragmentation, see page 505.) Hemorrhages may be seen either perivascularly or between muscle fibers.

In the rhodesiense infections, serous pericarditis and edema of the myocardium are usually present. Trypanosomes may be found in the pericardial fluid; with

Giemsa's stain a few trypanosomes are sometimes seen in the tissues, especially in the superficial epicardium. In the gambiense form a fibrous proliferation, largely perivascular, may be present beneath the endocardium or diffusely in the myocardium. Lesions similar to those found in man have been produced experimentally (Peruzzi, 1928).

Chagas' Disease. South American Trypanosomiasis. The chief manifestations of South American trypanosomiasis are seen in the heart and the central nervous system. The organism localizes in the cardiac muscle fibers, rupture of these fibers causes a myocarditis, and the lesion may be sufficiently widespread through the heart to cause death. Both children and adults are affected. A report by Packchanian (1943) that the vector is present in certain portions of southern United States suggests that some cases of cardiac disease in these areas may be South American trypanosomiasis.

The parasite is present in the blood as a trypanosome, when it enters the myocardial fibers it assumes a leishmanial form. These bodies are round or ovoid and measure from 1.4 to 4 micra in diameter, and each contains a large ruby-red nucleus and a rod-like or spherical deep violet kinetoplast. Within the myocardial fiber multiplication of the parasite occurs by binary fission. The parasites are present in large numbers in the fibers, the parasitized fibers may be unaltered, hyalinized or fragmented (Crowell, 1923). Parasitization of the fibers is not attended by inflammation, but upon rupture of the parasitized fiber, an inflammatory response usually occurs. This is characterized by lymphocytes, plasma cells, eosinophils and macrophages, and occasionally by neutrophils (Johnson, 1938). Muscle fibers may be separated by edema. In addition, it may be difficult to find the parasites within the inflammatory foci. The organisms may penetrate other muscle fibers as leishmania, or may enter the blood stream as trypanosomes. (See Figure X-2.)

Grossly, fibrinous pericarditis is often present, and the heart is pale; the myocardium may be flabby or firm. Punctate hemorrhages are seen and on section yellow streaks or areas of mottling may be present.

The existence of a chronic cardiac lesion in South American trypanosomiasis is still uncertain. In an important experimental study, Johnson (1938) produced active lesions in the dog, similar to lesions seen in man. In dogs that were allowed to live for several years, parasites could still be found within the myocardial fibers. The hearts of these animals also showed focal lymphocytic infiltrations and scattered areas of fibrosis. The fibrotic areas were most numerous in the myocardium adjacent to the endocardium and the epicardium, near the atrioventricular junction. Similar findings have been described by Decourt and associates (1947) in a person who was believed to have chronic Chagas' disease, and by Romana (1947).

Leishmaniasis. The leishmanial infections in man are of two types. *Leishmania donovani* is the causative agent in kala-azar, which is characterized by visceral lesions. Cutaneous or mucocutaneous leishmaniasis is the result of infection by *L. tropica (Oriental sore)* or *L. braziliensis* (American mucocutaneous leishmaniasis). As might be expected, myocardial involvement has been reported only in kala-azar, and in this disease it occurs only occasionally. The essential lesion of kala-azar is the proliferation of the reticulo-endothelial cells in response to the presence of the parasite, and the heart is not an important site of these cells.

Meleney in 1925 reported a fatal infection of kala-azar in a man of 23. Autopsy revealed a suppurative pericarditis, in addition to the usual splenic, hepatic and other specific lesions. On microscopic ex-

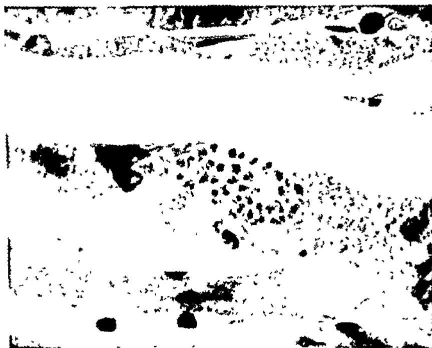


Figure X-2 *Trypanosoma cruzi* in heart muscle Iron alum, picric acid, hematoxylin stain. X 1285 (Courtesy of Morris Goldman, Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.)

amination of the heart, several areas of myocardial fragmentation were seen. In these areas were collections of inflammatory cells, including polymorphonuclear leukocytes, plasma cells, lymphocytes and clasmatocytes. Numerous Leishman-Donovan bodies were present within the clasmatocytes. No endothelial proliferation was noted.

Scattered foci of lymphocytes, polymorphonuclear leukocytes and macrophages have also been described (Lubitz, 1948) in cases in which no parasites were seen. The heart may be atrophic. While myocardial involvement may complicate the picture of kala-azar, it is not a major feature of the disease.

Malaria. All three forms of malaria, benign tertian (*Plasmodium vivax*), quartan (*Pl. malariae*), and malignant tertian (*Pl. falciparum*), show pathologic lesions related either to the phagocytosis of pigment by reticulo-endothelial cells or to the anemia resulting from destruction of the erythrocytes, falciparum malaria shows, in addition, lesions resulting from a concentration of parasites within the capillaries of organs with plugging of these capillaries by the parasitized red blood cells.

Benign tertian and quartan malaria. The principal changes and serious tissue lesions in the "benign" types of malaria result from the anemia produced by destruction of erythrocytes. The anemia causes parenchymatous degenerative changes, including fatty changes in the heart (Dudgeon and Clarke, 1917; Sprague, 1946) and fragmentation of myocardial fibers Phagocytosis of pigment is seen mainly in organs rich in reticulo-endothelial cells, changes related to the presence of pigment in other organs may be seen in severe infections but never reach the intensity of those found in the spleen and liver. In human malaria phagocytic cells are rarely encountered in the heart (Taliaferro and Mulligan, 1937).

When present, they are usually seen within capillaries. The phagocytic cells are probably circulating leukocytes, although it has been suggested that some may be capillary endothelial cells which may become phagocytic in exceptional circumstances. The pigment consists of discrete yellow-brown or black granules of uniform size or of larger irregular agglutinated masses within the cytoplasm of the cells (Ash and Spitz, 1945). In chronic lesions, the pigment may form free masses, following destruction of the phagocytic cells. When present in sufficient quantities, a gross brown to black slaty color may be imparted to the affected organ. Blocks for section should not be fixed in formaldehyde because formalin-precipitated hemoglobin may be confused with malarial pigment. Formalin pigment-granules are irregular in size and shape and are frequently crystalline.

Malignant tertian malaria. In addition to the pigmentation and the changes secondary to anemia, in falciparum malaria there are specific lesions caused by concentration of the parasites within the capillaries of the various organs There is, in general, a uniform distribution of the parasitized cells in the capillaries of such organs as the brain, heart, lungs and intestinal tract which are not rich in reticuloendothelial cells. The myocardial capillaries are distended with parasitized erythrocytes (Spitz, 1946). Ameboid forms of parasites may also adhere to the walls of the vessels and, at the bifurcations, clumps of ameboid forms may plug the lumen. Thrombi may be found in these vessels but are not always present. Parasites may also be found along the walls of larger vessels, particularly veins. The parasitized erythrocytes are often arranged as mounds which are present along the same side of the walls of different vessels, suggesting that some of the clumping observed in the vessels might represent a postmortem phenomenon (Spitz). In the heart, varying degrees of changes within the individual myocardial fibers are found. In some cases there is no change; in others there may be loss of striations with translucency of the cytoplasm. In some cases fatty degenerative changes are marked, which may be diffuse or irregular, the fat being present chiefly as fine droplets. Interstitial edema is frequently seen and small areas of hemorrhage, either interstitial or subendocardial, are also encountered. In occasional cases in which there has been a high parasite count, an irregularly distributed interstitial myocardial infiltrate may be found; the cells include lymphocytes, plasma cells and macrophages. The plugging of the myocardial capillaries with resulting anoxemic changes in the myocardial fibers constitutes a form of coronary occlusive disease (Merkel, 1946). The cause of the concentration of the parasites within the capillaries is not clearly understood. The possibilities of hemoconcentration, agglutination of parasitized red blood cells, or the presence of antibodies as factors influencing this phenomenon are discussed by Cannon (1941).

Malaria has not been proved to be a cause of chronic heart disease. Hyperplasia of collagen fibers and proliferation of young fibroblasts in the chronic malarial heart have been described (Galata, 1946).

Balantidiasis. A myocarditis caused by *Balantidium coli* was reported by Sidorov (1935). Histologically, *Balantidium coli* was found in the small arteries and also within the myocardium. There were foci of necrosis at the periphery of which were giant cells of the foreign-body type, lymphocytes, a few eosinophilic cells and many fibroblasts.

Infections by Parasites of Undetermined Nature

Toxoplasmosis. Myocardial involvement has been observed in nearly half of the re-

ported cases of *toxoplasmosis* (Callahan *et al*, 1946). Next to the central nervous system the commonest site of the infection appears to be the myocardium. Involvement of the heart in adult toxoplasmosis is a nearly constant finding, in infants lesions have been observed in the myocardium in 6 of 14 reported cases (Zuelzer, 1944). The parasites are found as agglomerations or as isolated organisms (Pinkerton and Weinman, 1940). There is no true cyst formation although occasionally a thin limiting membrane derived from the adjacent parenchyma may be present There may be a clear space surrounding the aggregate which is usually close to the nucleus of the fiber. The infected fiber is slightly swollen and may show partial loss of striations. The agglomeration varies in size according to the number of individual bodies which compose it; its size and shape appear to depend in part upon the nature of the tissue in which it develops. The largest masses occur in the cardiac muscle fibers and measure up to 50 x 10 micra. On the average, from 8 to 10 parasites are present but up to 60 have been observed The individual organisms appear as crescentic, ovoid or rounded bodies measuring 3 to 7 micra in length and from 2 to 4 micra in width. Dimensions of individual organisms vary, parasites that lie in loose tissue or are loosely packed are often larger than those found in denser masses In transverse section the organisms are circular The cytoplasm is clear, homogeneous and eosinophilic. The nucleus is fairly well demarcated from the cytoplasm, it is basophilic and may lie close to one end of the parasite In fixed material the nucleus is often irregular in shape. The nucleus occupies nearly the entire width of the organism In the myocardium there are also foci of necrosis, described as coagulation necrosis, with loss of myocardial fibers and infiltration of polymorphonuclear leukocytes, eosinophils and mononuclear cells (Paige *et al.*, 1942) Occasional parasites may be found in these necrotic foci Parasites may be found in fibers at the periphery of the necrotic areas or in fibers at a distance from the necrosis.

The parasites are apparently able to invade the fibers of the myocardium without destroying them or producing inflammatory reaction in the surrounding tissues. The organisms divide by binary division until the myocardial fibers are completely filled The myocarditis probably follows rupture of parasitized cells, the liberation of organisms inducing an inflammatory reaction in the surrounding tissue (Callahan *et al*, 1946). Other less prominent infiltrates of inflammatory cells may be scattered irregularly in the myocardium Although in some instances the myocardial lesions are not severe, in other cases they are extensive enough to produce signs of myocardial failure.

The changes described above are those of fatal cases. In chronic asymptomatic toxoplasmosis, a few scattered aggregates of parasites have been described in the cytoplasm of the myocardial fibers (Tomlinson, 1945) No foci of necrosis are seen in these instances and there are no noteworthy cellular infiltrates.

Differential points in the histologic diagnosis of toxoplasmosis have been given by Pinkerton and Weinman (1940) and by Perrin (1943)

Sarcosporidiosis. Cardiac involvement may occur in parasitization of man by Sarcocystis The organisms are found in cysts within scattered myocardial fibers. The cyst is an elongated oval mass measuring up to 0 19 mm in length (Hewitt, 1933). Within a well-defined, often striated outer membrane are enclosed numerous individual basophilic bodies, many hundreds may be found in a fully developed cyst (Craig and Faust, 1951a). Most of the parasites are round. In some instances no internal structure can be dis-

tinguished, in others a nucleus with a central karyosome may be recognized. There may be noted a difference between the central and peripheral parasites in a cyst, with the individual parasites separated into groups by prolongations from the cyst membrane The outer compartments contain "round cells," while in the inner fully developed compartments there occur the characteristic crescentic bodies called spores. The dimensions of these spores vary widely in the reported cases, from 2 to 16 micra. The involved myocardial fiber is usually slightly larger than the adjacent fibers. There is no necrosis or other evidence of reaction to the parasites. No cellular infiltrates are seen.

The organism must be distinguished especially from toxoplasma; the location in muscle only, the lack of inflammatory response, and the large number of individual parasites within a true cyst are distinguishing points (Kean and Grocott, 1945).

Helminthic Infections

Trichinosis. Myocarditis is a frequent and serious complication of trichinosis, often resulting in cardiac failure The myocardial lesions are caused by direct invasion of the myocardium by the circulating larvae. Following experimental feeding of trichinal larvae to rats, trichina embryos were found in the myocardium as early as five days after feeding. There is a marked inflammatory response to the presence of the parasite. The latter either is destroyed or escapes back into the circulation or into the pericardial sac. There is no encystment of the larvae within the myocardium, and there is no known chronic myocardial lesion resulting from trichinosis.

Macroscopically there are no constant findings (Gould, 1945). In many cases there may be parenchymatous degeneration of the heart but this is nonspecific and may be related to nontrichinal lesions present at the time of death. The pericardial fluid may be normal or may be increased in amount; it may be clear or blood-tinged. Trichina larvae may be found in the pericardial fluid. The myocardium may be fairly normal in appearance or may be pale, it ranges in consistency from firm to soft and flabby. Occasionally there is a yellow discoloration due to fatty changes.

Microscopically the lesion is essentially an acute interstitial myocarditis which is somewhat focal in distribution (Figure X-3) Some have found the lesion most marked just beneath the endocardium or epicardium (Gould). There are areas of focal necrosis of myocardial fibers with surrounding leukocytic infiltration The cells include polymorphonuclear leukocytes, lymphocytes, macrophages, plasma cells and eosinophils in varying proportions. The myocardial fibers are often vacuolated. There may be scattered small hemorrhages. In addition to these changes there are nonspecific degenerative changes.

The trichina larvae may be found within the foci of necrosis and leukocytic infiltration. Sometimes a well formed larva can be identified while in other cases only fragments of a parasite undergoing destruction remain (Figure X-4). The larvae measure from 80 to 120 micra in length. In sections they show a linear basophilic stippling Larvae may be found in the heart as long as 54 days after infection (Stryker, 1947). Gravid females have been found in the intestine of man 115 days after infection (Carter, 1950) With destruction of the larvae, the acute inflammatory process subsides. While it is possible that small foci of fibrosis may remain as a result of this inflammation there is no chronic cardiac lesion that is considered characteristic of trichinosis.

Trichuriasis. In man infection by *Trichuria trichiura,* the whip-worm, is practically always limited to the intestinal tract.



Figure X-3. Trichinous myocarditis X 175. (From Gould, S E *Trichinosis*, 1945, courtesy of Charles C Thomas)

The only effects upon the heart would be secondary and these are usually lacking since the intestinal infection is relatively asymptomatic or without general effects. Only one reference to possible general effects has been found. According to Getz (1945), "It seems certain that prolonged diarrhea and anemia may eventuate in cardiac failure and death. The role of massive infection with *T. trichiura* in the production of anemia remains unexplained "

Strongyloidiasis. Although the filariform larvae of *Strongyloides stercoralis* circulate in the blood stream before escaping into the pulmonary alveoli, the presence of the parasite elsewhere than in the respiratory and alimentary tracts is rare. Froes (1930) found rhabditiform larvae in the pericardial fluid of a 40-year-old man who also had massive pleural effusion containing larvae. The fact that the larvae were rhabditiform suggests that the patient harbored the adults in the pulmonary tissue, as may occur in some cases of strongyloidiasis.

The only report of myocardial lesions specifically caused by *S stercoralis* has been given by Kyle and associates (1948) A 47-year-old man with known strongyloidiasis had shown electrocardiographic changes interpreted as being due either to myocardial damage or to some extracardiac factor. No gross abnormalities of the heart or pericardial cavity were noted Sections of the heart, however, showed scattered filariform larvae surrounded by focal accumulations of lymphocytes in the pericardium and in the interstitial tissue of the myocardium

A pericardial location of larvae has also been reported in a chimpanzee by Blacklock and Adler (1922). Such isolated reports only emphasize the rarity of cardiac complications of strongyloidiasis.

Hookworm Disease. The cardiac lesions

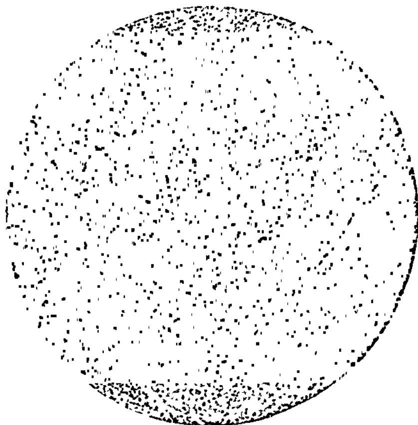


Figure X-4 Trichinous myocarditis Note fragments of larvae undergoing destruction Trichinae larvae are unable to encyst in the heart. (From Gould, S E *Trichinosis,* 1945, courtesy of Charles C Thomas.)

in patients infected with hookworms are nonspecific. There is no report in which either the adult worm or its larval form has been found in myocardial or pericardial tissues The gross anatomic change in the heart of the hookworm patient is cardiac enlargement This change is caused by one of three factors: a reducible dilatation, a dilatation and hypertrophy, or a hypertrophy unassociated with a reducible dilatation (Porter, 1937). The chief factor in this cardiac lesion is believed to be anemia resulting from mechanical loss of blood from the intestinal tract at points of attachment of the adult parasites. The changes in the heart are the same as those seen in other types of anemia in man and in those induced experimentally. The primary cardiac dilatation is a physiologic adjustment which disappears when the anemia is relieved; if the factors continue, hypertrophy results. The changes are found both in the left and the right ventricles. Murmurs present may be partially hemic but also may be the consequence of a relative mitral insufficiency or a functional supra-valvular pulmonary stenosis. In one series of cases of cardiac enlargement associated with hookworm infection, 90 per cent of the patients showed relief of signs of cardiac involvement paralleling improvement of the erythrocytic and hemoglobin levels; in these patients the intestinal hookworm infestations were persistent and untreated (Heilig, 1942). The remaining patients showed no change in the pathologic heart condition before deworming; in these cases the heart dilation and other myocardial signs improved quickly after elimination of the parasites. For this reason it is postulated that there is a second pathogenic factor which is de-

pendent on the presence of the adult worm. It is questioned whether this second factor is a toxin or an allergen; the eosinophilia characteristic of hookworm disease might indicate the latter.

Nonspecific microscopic findings have been reported in the hearts of patients infected with hookworms (Sanabria, 1945). These findings include interstitial edema, fatty and parenchymatous degeneration of myocardial fibers, local and diffuse foci of polymorphonuclear leukocytes, plasma cells and eosinophils, and small foci of fibrosis. In those hearts in which the enlargement has been present for a long time there is also hypertrophy of myocardial fibers. Hydropericardium has been described (Carrillo, 1946).

Acanthocheilonemiasis. Although pathologic studies in man infected with *Acanthocheilonema perstans* are lacking, the related parasites in monkeys may be found in the pericardium and other serous cavities. The worms "sew" themselves into the serous membranes where they cause local irritation, often with a resultant fibrinous exudate (Craig and Faust, 1951b)

Heartworm Disease. The only cardiac involvement by filarial worms in man that has been reported is the rare occurrence of the heartworm. Two such cases have been described. The first of these was reported by de Magalhães in 1887. A single male and a single female filaria were found in the left ventricle of a boy In 1941, Faust and associates reported finding a mature male filaria in the inferior vena cava of an elderly Negro woman who had always lived in New Orleans In both cases, the infecting worm was identified as a member of the genus Dirofilaria. (See Figure X-5)

Schistosomiasis. Specific cardiac lesions in schistosomiasis may occur either as a result of localization of the larval or adult worm in the heart, or of infiltration of eggs which have been deposited by the adult worm at the usual intestinal or vesical sites. Metastatic localization of the eggs occurs in the liver chiefly, in the lungs and brain infrequently, and in the heart occasionally. A cardiac lesion secondary to pulmonary schistosomiasis is also described.

Localization of an adult worm within the heart has been reported on only one occasion (El Gazayerli, 1939). In a man of 24 years who showed schistosomiasis of many viscera, an adult male worm was found in the circumflex branch of the left coronary artery. The worm appeared intact and lay free in the lumen No ova were present in the heart. The possibility was considered that the cercariae had developed into adult worms in the pulmonary vessels

The lesions caused by deposition of eggs in the myocardium are essentially the same as those found in the intestines, urinary bladder and liver. Faust (1948) has described these lesions, microscopically they present the picture of a pseudo-tubercle, with individual eggs as the centers of a tissue reaction Adjacent to the egg there is an area of lipid and coagulation necrosis of local tissue cells Around this zone of necrosis there is an envelope of macrophages, epithelioid cells and giant cells; while infiltrating the area more peripherally are large numbers of eosinophils, plasma cells and lymphocytes, and occasional neutrophils. In the acute phase, the character of the cellular infiltrate may vary; sometimes a higher proportion of eosinophils is found. Tiny abscesses with necrosis have been described by Thomas and associates (1946). In one case, these authors noted thrombosis and hyalinoid necrosis of arterioles and venules with widespread necrosis of the ventricular septal myocardium. As the lesion becomes more chronic, there is an infiltration of fibroblasts and fibrocytes. The end result is a complete fibrotic encapsulation of the egg. During this process the egg has be-



Figure X-5 Heartworm (*Dirofilaria immitis*) infection in dog (Courtesy, Armed Forces Institute of Pathology, Neg 108,784)

come nonviable and may eventually be calcified. The eggs are seen in the acute phase as oval eosinophilic masses measuring 35 to 70 micra, containing irregularly scattered coarse basophilic chromatinic material, and being separated from the chitinous shell by a clear space.

The deposition of eggs in the myocardium, although reported several times, is nonetheless uncommon Jaffé (1943) found only one instance of such deposition in more than 400 autopsies on patients with schistosomiasis, and in Hutchison's discussion (1928) of the pathology of schistosomiasis, the heart was given no mention.

Right ventricular hypertrophy is another cardiac lesion resulting from human schistosomal infection. This lesion is more frequent in occurrence and probably more important although it is secondary and nonspecific. The right ventricular hypertrophy is associated with chronic pulmonary arteritis resulting from schistosomal infection This cor pulmonale with gross dilatation of the pulmonary artery is by no means a rare clinical finding in Egypt (Clark and Graef, 1935; Day, 1937, Bedford *et al.*, 1946). The lesions may be caused by *Schistosoma hematobium* but usually are caused by *Schistosoma mansoni* (Kenawy, 1950). The disease is frequently encountered in young adults suffering from advanced visceral schistosomiasis or from severe genito-urinary schistosomal infection. The ova reach the lungs as emboli from the normal habitat of the worms and become impacted in the

pulmonary arterioles or escape from the capillaries into the alveolar spaces. In either instance, they form granulomatous pseudo-tubercles as previously described, with the eventual formation of fibrous nodules. Vessels involved by the granulomatous inflammation are chiefly the arterioles and the result is either a necrotizing arteriolitis or a constricting periarteritis There is an increase of pressure in the pulmonary arteries and a resultant hypertrophy of the right ventricle and development of arteriosclerosis of the pulmonary arteries. In some cases an incompetence of the pulmonary valves occurs.

The existence of a chronic myocardial schistosomiasis has been reported, especially by Jaffé (1937) However these studies lack anatomic verification of the specific nature of the myocardial lesion and in Jaffé's autopsies less than ¼ of 1 per cent of his cases revealed the presence of eggs in the myocardium.

Heterophydiasis. Cardiac involvement in various types of intestinal heterophydiasis has been reported by Africa and associates (1935, see Craig and Faust, 1951c, d) The heart was involved by eggs of the following trematodes: *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Haplorchis yokogawai*, *Haplorchis pumilio*, *Haplorchis taichui*, *Diorchotrema pseudocirratum* and *Heterophyes brevicaeca*. Clinically the patients revealed cardiac failure. Grossly the hearts were edematous and there were subepicardial hemorrhages, especially on the right side. The gross changes were similar to those of beriberi. Microscopically the eggs of the various trematodes were found in spaces between cardiac muscular fibers. Capillaries were intensely injected. The intestinal tissues were edematous and there was fragmentation of many of the muscle fibers. Small pericapillary hemorrhages were believed caused by rupture of the capillaries by the eggs. There was a lack of inflammatory and proliferative changes in these hearts. The authors believed the changes to be the result of embolism of the eggs from the adults in the intestines. They considered their findings to constitute another factor in the etiology of heart failure

An adult heterophyid has been found in the epicardial layer of the heart (Craig and Faust, 1951d)

Cysticercosis. When man is the intermediate host in infection with *Taenia solium*, the cysticerci may be found in any tissue of the body, including the heart. Localization in the heart, however, is unusual (Menon and Veliath, 1940) The cysts may vary from 0.5 to 3 cm. or more in diameter They are usually multiple and may be located within the musculature or beneath the endocardial or pericardial surfaces. In general they are round except in the deeper portions of the muscle where they tend to be elongated Around the thin glistening cyst wall a pale thin fibrous capsule can be seen. The muscular bands appear to be separated by the cysts. In some of the cysts the scolex can be recognized Microscopically the cyst wall typically has three zones. The inner zone is composed of dead and disintegrating leukocytes and large mononuclear cells, foreign-body giant cells and foam cells may also be present, and occasionally cholesterol clefts may be seen The middle zone shows fibroblastic proliferation and plasma cells. The outer zone contains vascular granulation tissue, polymorphonuclear leukocytes and a few eosinophils. The scolices may be well preserved or may show partial disintegration. Suckers and hooks may be perceptible The larvae may become necrotic and eventually undergo calcification

Echinococcosis. The incidence of primary hydatid cysts of the heart is very low. The Australasian Hydatid Registry includes only six cases of cardiac hydatid

cysts in over 1800 cases of hydatid disease (Cole, 1947). In Iceland two instances of cardiac hydatid cysts were found in 60 cases of echinococcosis among 1200 autopsies (Dungal, 1946). Dew (1928) states that hydatid cysts of the heart comprise 1 to 1 5 per cent of all primary hydatid cysts. Peters and associates (1945) reviewed 61 cases of echinococcal infestation of the heart They pointed out that echinococcal infestation of American cattle seems to be increasing, and a similar increase may be present among sheep and hogs This increase may well be reflected, sooner or later, in the appearance of human cases of echinococcal infection acquired in the United States. Early recognition of cardiac echinococcosis is important since the lesion is amenable to treatment

In a majority of cases hydatid cysts of the heart are primary, having developed from the hexacanth embryo which, after traversing both the hepatic and pulmonary capillaries, is carried to the heart muscle by the coronary arteries (Dew). In some instances attachment may be directly to the endocardial surface, with subsequent growth into the cardiac tissue The embryo usually comes to rest in the muscle of the ventricle or atrium and the resultant cyst may grow toward the chamber of the heart or may project under the visceral pericardium It is at first simple and may remain quiescent for a long time before some complication occurs or it is discovered either on roentgenologic examination of the chest or at autopsy. Primary cysts are probably always solitary. Multiple cardiac and pericardial cysts have been described but it is almost certain that all these cysts are in reality secondary to the rupture of a primary cyst. The right ventricle has been most frequently infected, although the cyst may develop under the endocardium or pericardium or in the muscular wall of any of the cardiac chambers. Secondary cysts are much more common in the right side of the heart. Hydatid cysts are at first simple and univesicular with a well defined adventitia which, however, tends to become thinned out when the cyst projects into the endocardium or pericardium (Schroeder and Medoc, 1945). Death or degeneration of the parasite may occur and the contents of the cyst become caseous or inspissated. It is possible that in this way healing may occur. Usually, however, as a result of constant increase in the size of the cyst and to the continual trauma of muscular contraction, spontaneous rupture occurs either into the pericardium or into one of the chambers of the heart. Rupture occurs more frequently into the right cardiac chambers; this has been related to the lower pressure found in these cavities. At the time of rupture of the primary cyst, death may occur from anaphylaxis resulting from sensitization to hydatid proteins. If rupture has occurred into a cardiac chamber, death may also occur from pulmonary or cerebral embolism by the liberated material. If death does not occur, there is frequent growth of secondary cysts in the lungs or in other peripheral organs, especially the brain. These secondary cysts characteristically have approximately the same size.

About 10 per cent of all primary cardiac cysts rupture into the pericardial sac. As a result of this rupture, the brood capsules and scolices are shed into the pericardial cavity and are there implanted. Some are destroyed by an inflammatory reaction, with resultant thickening of the serous membrane and the formation of adhesions. Others, however, survive and develop into secondary cysts which are multiple and are approximately of the same size. These cysts may become covered by a membrane continuous with the pericardium.

Following rupture of the primary cyst,

it may undergo involution and fibrosis but more commonly the rent in its wall becomes healed and daughter-cyst formation occurs from the residual germinal elements. These daughter cysts in turn may rupture. Rupture of daughter cysts usually causes sudden death.

Grossly, hydatid cysts vary in size from a few micra to 1 cm. or more in diameter. There is compression of the adjacent parenchyma. The cyst itself has a chitinous wall and has a content of smaller cysts, the daughter cysts, and of brood capsules and hooklets, forming the so-called hydatid sand. The daughter cysts are thin-walled and frequently lie free within the cyst fluid. Microscopically there is found the compressed fibrous tissue of the organ in which the cyst lies, this forms an outer wall. The external portion of the cyst proper is an acellular laminated chitinous layer Within this is the germinal membrane to which may be attached brood capsules containing the invaginated scolices Hooklets may be found free in the fluid of the cyst A foreign-body reaction may be found in the wall of the younger cysts, this has been related to leakage of hydatid fluid Pseudo-tubercles may also form around degenerated scolices.

Diagnosis of a cardiac hydatid cyst has been made by roentgenologic examination (Zizmor and Szucs, 1945).

Sparganosis. *Sparganum proliferum* is a proliferating larva of a pseudophyllidean tapeworm, the adult form of which is unknown. These larvae have been recovered from the heart as well as from other tissues of man (Craig and Faust, 1951e)

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CHAPTER XI

Injuries of the Heart and Pericardium by Physical Violence

ALAN R. MORITZ

INJURIES OF THE HEART by mechanical violence may be disruptive or nondisruptive, primary or secondary. If the cardiac injury represents the effects of force that has been applied or transmitted to the heart, it may be characterized as primary The manifestation of such an injury may be functional, structural or both. If the cardiac disturbance is due to disruptive or functional changes that have been produced elsewhere in the body by the action of mechanical violence, the cardiac injury may be characterized as secondary. So far as the heart is concerned, such secondary disturbances are characteristically functional

THE DIRECT OR PRIMARY EFFECTS OF PHYSICAL VIOLENCE ON THE HEART

Penetrating Injuries

Force responsible for penetrating wounds of the heart reaches that organ in two principal forms, *i.e.*, as a flying missile or as a slender rigid object. Bullets and shell fragments constitute the majority of the former. Slender rigid objects, other than knives, that may be responsible for stab wounds of the heart include the sharp end of a broken rib (Figure XI-1), an ice-pick, a sharpened file, a stiff wire, a long pin or needle, a sharp splinter of glass, wood or metal, and others too numerous to mention. In the majority of penetrating injuries of the heart, both civilian and military, the external wound is anterior thoracic and lies in an area bounded by the clavicle above, the tip of the xiphoid below, the costochondral junctions of the sternum on the right and the anterior axillary line on the left (Hardt and Seed, 1942). The practical importance of this location with reference to the use of body armor by soldiers and other persons in similarly dangerous occupations is obvious.

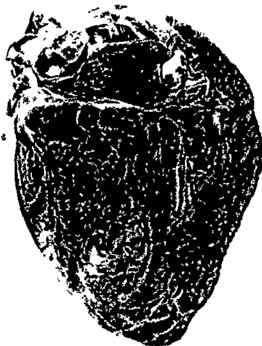


Figure XI-1 Stab wound of apex of right ventricle by end of broken rib

One of the most significant differences between cardiac wounds produced by stabbing and those produced by bullets is related to the fact that a bullet ordinarily travels at much higher velocity than a knife and, therefore, possesses more kinetic energy Thus, a bullet that grazes or passes close to the heart may be capable of liberating a great amount of energy to the tissues and often causes more extensive injury than would be expected from the size and course of the missile It is not unusual for a heart through which a small high-velocity projectile has passed to be extensively disrupted (Figure XI-2). Widely disseminated foci of cardiac injury may result from the energy liberated by a bullet that has passed through the body in the vicinity of the heart

A knife-thrust ordinarily occurs at relatively low velocity and its damaging effects tend to be local. Knife wounds of the heart, even though they are transmural, tend to close when the knife is withdrawn, whereas the passage of even a small high-velocity bullet through the heart may result in rapid and copious bleeding.

The remarkable propensity of the myocardium to effect partial closure of a transmural defect by its own turgor deserves emphasis. Hillsman (1947) has observed in the case of small transmural wounds, both atrial and ventricular, that the bleeding characteristically occurs in small spurts and only during systole. It is this phenomenon that often enables persons who have sustained penetrating wounds to survive long enough to have successful surgical repair of the defect. It also explains how persons with relatively large penetrating wounds of the heart are sometimes capable of astounding physical feats prior to collapse and death.

The consequences of a penetrating wound of the heart fall into three principal categories dysrhythmia, hemorrhage and infection

Dysrhythmia. Conduction disturbances caused by disruptive cardiac trauma vary from such reversible and relatively insignificant phenomena as extrasystoles or bradycardia to almost immediately fatal asystole or ventricular fibrillation Such functional disturbances are frequently out of proportion to the structural evidence of the injury. A more complete discussion of traumatic cardiac dysrhythmia will be found on page 862.

Hemorrhage The most common mechanism of disability and death following a penetrating injury of the heart is tamponade. If blood collects in the pericardial sac more rapidly than it can be evacuated through the defect in the pericardium, intrapericardial pressure eventually rises to such a height as to collapse the great veins, thereby preventing the return of blood to the heart (Figure XI-3). The time required for the development of tampo-



Figure XI-2 Large gaping wound in left ventricle produced by high velocity 22 calibre bullet

nade varies from a few seconds to many hours, according to the rapidity of the bleeding and the patency of the defect in the parietal pericardium. The amount of blood that can be tolerated in the pericardial sac without tamponade probably varies considerably from person to person and tends to bear an inverse relation to the speed with which it accumulates. If the accumulation is rapid, not more than from 300 to 400 ml. can be tolerated (Figure XI-4). That larger effusions can be tolerated if the accumulation is slow is indicated by the occasional finding at autopsy of a hydropericardium containing as much as 1000 ml.

The absorption of extravasated blood from the pericardial sac by way of the lymphatics is exceedingly slow. The cellular components of the intrapericardial blood tend to organize at sites of endothelial damage and may or may not result in adhesions between the surfaces. Pigment-containing macrophages may be found at the site of organized hematomas after many months.

If the defect in the parietal pericardium is large, death may result from exsanguination rather than tamponade. In such circumstances most of the escaped blood collects in the pleural cavities and the amount lost externally is relatively small.

Infection. Before the introduction of antibiotics, purulent pericarditis (Figure



bullet which grazed proximately six hours ricardial sac to cause fatal tamponade

XI-5) was the most important complication of a penetrating wound of the pericardium, if the immediate effects of shock and hemorrhage were survived.

Effects of Pleural and Pericardial Injuries on the Heart. Frequently, although not invariably, a penetrating cardiac injury will be accompanied by wounds of the pleura or lungs If the immediate effects of the cardiac injury are survived, such wounds may lead to the development of pneumothorax or interstitial mediastinal emphysema, either of which may embarrass the heart by displacement or compression. Entrance of air into lacerated pulmonary veins may lead to coronary and cerebral air embolism.

Healing of Penetrating Injuries of the Heart. Hesse and Hesse (1924) have observed that the blood clot filling a traumatic myocardial defect, even though it be small, is slow to resorb or organize. Significant fibroblastic invasion of the margin of a myocardial hematoma, according to them, is not seen much earlier than a week The formation of granulation tissue first occurs at the site of the epicardial defect and is seldom well developed under two weeks Fibroblastic proliferation along the transmural portion of the tract

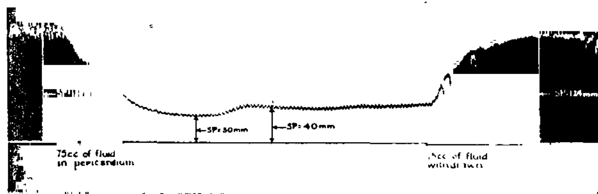


Figure XI-4 Cardiac tamponade produced within 30 seconds in dog by the injection of 75 ml. of saline into the pericardial sac Systolic blood pressure (S P) fell from 130 to 30 mm. of Hg due to pressure on the great veins and atria Four minutes later the tamponade was relieved by withdrawal of the saline and the blood pressure returned to normal

is minimal. Although occasional multinucleated cells indicate a reactive hyperplasia on the part of the injured muscle cells, there is relatively little regeneration. After a month it is difficult to recognize the intramural portion of a penetrating cardiac wound except by the presence of small epicardial and endocardial fibrous plaques at the sites of entrance (Figure XI-6) and exit.

Foreign Bodies. The position of the bullet as disclosed by roentgenologic examination of a person who has sustained thoracic injury by gunfire may be grossly misleading in respect to establishing the probability of cardiac injury. Bullets that have wounded the heart may strike the spine or a rib and ricochet to a remote position Bullets that have entered the heart may be swept out of that organ by the systolic discharge of blood, to be carried into a pulmonary or peripheral artery. A bullet that has entered the precordium at an angle may strike a rib and ricochet to a position behind the heart without damage to that organ.

In nine of 11 cases of intracardiac foreign body reported by Harken and Williams (1946), a bullet found in the right ventricle had first entered a systemic vein and had then been carried to the heart by way of the blood stream. In two instances bullets had been carried through the right chambers of the heart and had come to rest in a pulmonary artery. Although metallic foreign bodies situated in the pericardial sac or in the outer portion of the myocardium tend to become en-



Figure XI-5. Purulent pericarditis following the successful suture of a transmural ice pick wound of the pulmonary conus.

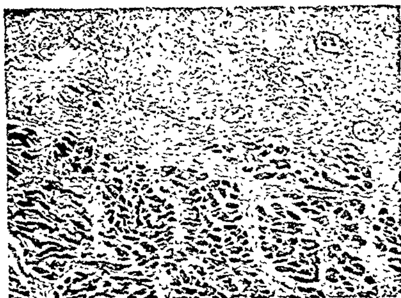


Figure XI-6 Subepicardial cicatrix at the site of a healed (many months) laceration of the wall of the left ventricle. Hematoxylin-eosin X 100



Figure XI-7 Two lead shot that resided for 27 years in the wall of the right ventricle There were no pericardial adhesions, no epicardial scars and no residual hematogenous pigmentation Each pellet was enclosed in a thick fibrous capsule

capsulated by fibrous connective tissue and are often tolerated indefinitely without further disturbance (Figure XI-7). Harken and Williams believe that large foreign bodies (1 cm. or more in each of two diameters) within the heart constitute a potential hazard to health and life Such a foreign body, according to them, may be mobilized as an arterial embolus (pulmonic or systemic) or, if it remains within the heart, tends to predispose to the development of subacute bacterial endocarditis. Decker (1939) believes that the danger of migration, perforation and tamponade is an added reason for undertaking the surgical removal of a sharp foreign body.

Needles and similar pointed objects that enter any portion of the body and eventually migrate into a systemic vein may be carried to the right side of the heart. Here they may become embedded in the wall of the right ventricle or be carried through the chambers to become a pulmonary embolus. As an incidental postmortem finding, the author has seen (1) part of a hyperdermic needle, that had been broken off in an arm many years before, embedded



Figure XI-8 Phonograph needle projecting into the chamber of the left ventricle from a cicatrix in the interventricular septum The needle had probably entered a systemic vein and had been carried in the blood stream to the right ventricle where it became embedded in and migrated through the interventricular septum

in an organized non-occlusive mural thrombus in a branch of the right pulmonary artery; and (2) a phonograph needle, that had entered the body at an unknown site at an unknown time, embedded in the interventricular septum (Figure XI-8) In both instances the foreign body had been tolerated without clinical evidence of its presence and without pathologic evidence of progressive injury

A more important type of migrating foreign body is the sharp object that has been swallowed and that has penetrated the parietal pericardial sac by way of the anterior wall of the esophagus. The author has seen two such foreign bodies (a pin and a fishbone) that had migrated in this manner and resulted in purulent pericarditis.

Blunt Injuries of the Heart and Pericardium

Of primary importance to a consideration of cardiac injury by blunt violence is the fact that during the first five decades of life the thoracic cage is usually sufficiently plastic to permit great distortion without fracture. Thus, an impact may produce severe injury of the intrathoracic viscera without damage to the ribs or sternum. In a series of non-penetrating chest injuries sustained in 168 instances by a fall from a height, in 38 instances by the impact of a falling or swinging object, and in 28 instances by a squeezing or crushing force, Arenberg (1943) observed that the incidence and severity of cardiac injury were less in persons who had suffered broken ribs than in those whose thoracic cage was unbroken. It may be inferred that thoracic rigidity is an important factor in protecting the heart against injury by blunt violence.

Preliminary to a consideration of cardiac injury by blunt impact, it should be appreciated that hydrostatic forces transmitted to the heart by way of the great vessels may increase the bursting tension within that organ to the point of rupture (Figure XI-9). A crushing injury of the abdomen and lower extremities may displace blood toward the heart with sufficient force to rupture the intrapericardial portion of the thoracic aorta, lacerate valves or cause an explosive type of disruption of the wall of the left ventricle or atrium (Moritz, 1942). Cardiac injury caused by the application of blunt violence to the thorax falls into three groups, according to the severity of the disruptive changes: *commotion, contusion* and *laceration.*

Cardiac Commotion. Cardiac commotion denotes a disturbance in cardiac function that has been caused by impact or agitation of that organ without the production of gross or microscopic evidence of injury. That the functional disturbance caused by an impact to the heart may be disproportionate to the morphologic evidence of injury has long been recognized (Kulbs, 1909). It is a fact that a precordial impact may result in a severe and even a fatal disturbance in the function of what may appear to be an undamaged heart.

Without the benefit of a direct examina-

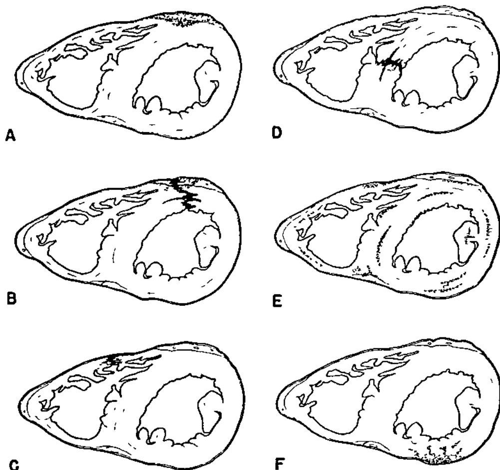


Figure XI-9 Various types of cardiac injury which may result from non-penetrating thoracic impacts.

A. Anterior contusion,
B. Laceration of left ventricle,
C. Laceration of right ventricle,
D. Laceration of interventricular septum,
E. Disseminated non-communicating lacerations of myocardium,
F. Posterior contusion

(From Moritz, A R *Pathology of Trauma* Philadelphia, Lea & Febiger, 1942 Reproduced by courtesy of publisher)

tion of the injured heart the clinical observer has no way of recognizing the extent to which the observed functional disturbance may be accompanied and explained by disruption of structure. Usually the most that can be said on the basis of history and clinical examination is that cardiac dysfunction developed immediately after, and presumably as the result of, an external impact. The fact that a posttraumatic functional disturbance of the heart is transient does not indicate the absence of structural change, any more than the fact that when it is fatal it requires the presence of a visible structural lesion.

There is ample evidence from animal experimentation to support the conclusion that the force of a blunt impact to the chest may cause a wide variety of nonfatal and fatal disturbances in cardiac function without visible evidence of injury (Bright and Beck, 1935, Schlomka and Schmitz, 1933, Kulbs, 1909; Kastert, 1939).

In a series of dogs in which the heart was exposed and subjected to non-fatal blunt impact, Moritz and Atkins (1938) found that structural evidence of cardiac injury was absent in three of five animals that developed posttraumatic extrasystoles, in one of two that developed bradycardia, in two of six that developed tachycardia and in two of seven that developed ventricular fibrillation.

Since it is rarely possible to make a direct examination of the heart of a human subject who has recently suffered a non-fatal cardiac injury, the frequency with which such transient posttraumatic cardiac disturbance occurs independently of structural lesions is not known That transient posttraumatic disturbances in cardiac function in man following impact to the chest are not uncommon is indicated by the reports of White and Glendy (1941), Barber (1944), and Bright and Beck (1935) A few reasonably well-documented instances of death of human subjects from heart failure following blunt injury of the chest, in which neither gross nor microscopic evidence of cardiac injury was disclosed by postmortem examination, have been reported (Barber, 1944; Warburg, 1938; Hedinger, 1944).

Certainly the evidence purporting to establish that the failure of an apparently uninjured heart has resulted from the direct effect of mechanical violence should be examined most critically. The requirement proposed by Kahn and Kahn (1929) that the signs and symptoms of cardiac dysrhythmia should develop immediately after the trauma in order to be consistent with a cause-and-effect relationship should be regarded as minimal.

The mechanism responsible for such functional disturbance is obscure. Schlomka and Schmitz, and also Kastert, on a basis of animal experiments, concluded that the cardiac disturbances caused by commotion are probably due to reflex coronary vasoconstriction and myocardial ischemia. In support of this theory, Kastert reported the finding of focal areas of myocardial degeneration and necrosis in relation to the coronary termini in animals that had survived the immediate effects of a non-disruptive cardiac impact. Muller (1942) described disseminated foci of ischemic change in traumatized human hearts. Kartagener (1946) after a clinicopathologic study of the problem doubted the occurrence of traumatic vasospasm unless the coronary arteries were already the seat of atherosclerosis. That coronary disease may increase the susceptibility of the heart to trauma receives some support from the early experiments of Külbs and Strauss who observed that rabbits having cholesterolosis of the coronary arteries were less tolerant of thoracic impacts than normal animals.



Figure XI-10 Explosive laceration of left ventricle due to hydrostatic force developed during impact from fall from height

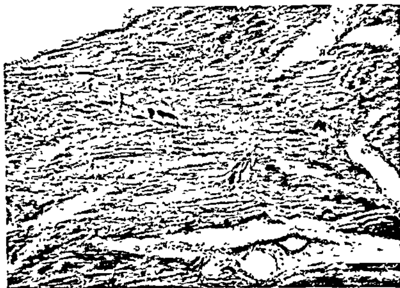


Figure XI-11 Diffuse interstitial extravasation of erythrocytes at the site of a posterior myocardial contusion Death occurred several hours after blunt injury of chest Hematoxylin-eosin X 100

Cardiac Contusion and Laceration. A *contusion* is a diffuse extravasation of blood into the interstitial spaces caused by impact (Figure XI-11). The minute vascular defects through which blood escapes may be created by excessive distortion or stretching of the tissue or by a sudden rise in intracapillary pressure due to the hydrostatic effects of sudden compression

If only the heart is examined it may be difficult or impossible to distinguish between contusion and certain nontraumatic interstitial extravasations of blood. Subendocardial and subepicardial hemorrhage are frequently encountered when death has been preceded by an agonal period of asphyxia or anoxia or when death has been caused by some powerful systemic poison such as arsenic. Persons dead of hyperthermia frequently reveal spontaneous hemorrhages beneath the endocardium If an interstitial extravasation of blood represents a contusion it should be localized to the heart and such other structures as were in the path of force, whereas if the bleeding was spontaneous and the result of a systemic disorder it is not usually confined to the thoracic viscera. Another type of nontraumatic interstitial hemorrhage that may simulate cardiac contusion is an early infarct The true nature of such a lesion is ordinarily disclosed by the finding of the occluded vessel and the presence of a central zone of ischemic necrosis.

A *laceration* is a gross defect in the continuity of tissue caused by a crushing or stretching force and, although it may or may not be associated with contusion, it is almost invariably associated with hemorrhage An exception to this rule is a laceration of the chordae tendineae, inasmuch as these structures are normally avascular

At first glance, it may be impossible to distinguish between a traumatic rupture of the heart and a spontaneous rupture due to disease. Although the heart may be ruptured by a precordial impact, spontaneous rupture at the site of a recent myocardial infarct occurs more commonly. Should an infarct rupture, it usually does so within 3 to 10 days after its development. The true nature of such a lesion

may not be recognized until either the site of vascular occlusion is located or microscopic examination discloses changes indicative of antecedent necrosis. That cardiac rupture at the site of an infarct may take place in ambulatory persons not previously recognized to be suffering from heart disease, has been emphasized by Jetter and White (1944).

Impacts responsible for disruptive cardiac injury are usually sustained over the precordium and may or may not be associated with fractures of the sternum or ribs Although a fall from a height is the most common traumatic cause of cardiac rupture, a wide variety of trauma has been reported in the literature Beck has emphasized the importance of the steering-wheel impact in which the driver is thrown forward by the sudden deceleration of his vehicle It should be borne in mind that the object responsible for the fatal precordial impact may not be immediately recognized. A man recently found dead on the floor of a factory was thought to have died of spontaneous cardiac rupture due to infarction but at autopsy it was discovered that his cardiac lesion was undoubtedly of traumatic origin. It was subsequently learned that he had been working on a piece of wood, this had become jammed in a circular saw and was then hurled against his chest, causing immediate death. The piece of wood was later found at a considerable distance from the point at which he had fallen.

Cardiac contusions and lacerations resulting from blunt injury may be anterior and directly beneath the site of the external impact or may be remote from it. Injuries due to anterior thoracic trauma are sometimes found in the posterior wall of the heart, presumably due to the impact of the heart against the vertebral column. According to Urbach (1922), the distribution of cardiac lesions resulting from blunt impact arranged in order of diminishing frequency are right atrium, left ventricle, right ventricle, left atrium, interventricular septum and valves.

The experimental findings of Moritz and Atkins (1938) suggest that the hydrostatic force incident to sudden compression of the heart between the sternum and ribs anteriorly and the vertebral column posteriorly is a frequent cause of rupture. Lateral displacement of the heart by an obliquely directed force may lacerate the pericardium without damage to the heart or may tear the wall of the left atrium at the ostia of the pulmonary veins. In the case of cardiac laceration incident to a fall from a height, partial or complete circumferential laceration of the aorta immediately above the aortic valves is sometimes encountered.

It has been observed both in man and in experimental animals that a blunt injury of the heart may lead to widely disseminated myocardial hemorrhages without visible laceration These are apparently the result of minute focal lacerations of muscle and probably result from an impact delivered while the ventricles are filled with blood. Both Munck (1937) and Warburg (1938) have stressed the frequency of this type of injury in human subjects

Posttraumatic Dysrhythmia. It appears that many if not most of the functional disturbances of the heart that have been observed in animals following blunt impact to the precordium may follow cardiac trauma in man. In a series of experiments reported by Kulbs and Strauss (1932), bradycardia with extrasystoles was observed after single non-fatal impacts. In animals suffering from previously induced cardiac abnormality (aortic regurgitation, coronary cholesterolosis, digitalis poisoning, thyroxin poisoning), the posttraumatic disturbances in rhythm were often accompanied by acute cardiac dilatation and terminated in death.

In experiments by Schlomka and Schmitz (1933) there were posttraumatic changes in the QRS and T waves and bundle branch block, the changes being similar to those which result from coronary insufficiency. The electrocardiographic disturbances were accompanied by a drop in arterial pressure, a rise in venous pressure, and right-sided dilatation. Bright and Beck (1935) exposed the heart in dogs and subjected it to direct impact of a metal hammer. There was often an immediate and extreme rise in pulse rate with falling arterial and rising venous pressures In experiments on survival, cardiac dilatation often persisted for several weeks. The electrocardiographic changes were similar to those reported by Schlomka and Schmitz, and their disappearance tended to parallel the reduction in size of the cardiac silhouette.

That a similar range of functional disturbances may occur in man following thoracic trauma is indicated by the numerous case reports included in the reviews written by Bright and Beck, Glendy and White (1936), Warburg and Barber

Tamponade. Unlike the relatively slow bleeding so often observed after penetrating injuries of the cardiac chambers or of the epicardial vessels, hemorrhage following the type of cardiac laceration characteristically caused by blunt impact is usually so rapid as to be fatal almost immediately. The author knows of no authentic instance of survival after the occurrence of a transmural cardiac laceration by blunt force.

Myocardial contusions heal readily if the immediate functional effects of the injury are survived, and within a week the interstitial extravasation of blood is absorbed with little or no residual abnormality. The persistence of functional disturbances for more than a few days after injury should, in the absence of hemopericardium or a suddenly acquired valvular insufficiency, cast doubt on the traumatic origin of the disturbance.

Injuries of the Valves. The cardiac valves, their chordae tendineae and their papillary muscles, may be lacerated by precordial impact, by hydrostatic force transmitted from sites of trauma elsewhere in the body or by the strain of overexertion. According to Glendy and White (1936), nearly all ruptured valves are found at autopsy to have been the seat of antecedent disease

The largest series of traumatic rupture of normal valves is that reported by Adam in 1927 and includes 15 cases Of these, seven were of the aortic, five of the mitral, one of the aortic and the mitral, two of the pulmonic and one of the tricuspid In 1928 Howard collected 112 cases of valvular rupture but this series included both diseased and normal valves. White and Glendy (1941) have stressed the importance of being most critical of the evidence purporting to establish that a diseased valve has become insufficient because of trauma. Unless it can be shown that the valvular insufficiency developed after, and not before, the trauma and that the trauma or stress was of such a nature as to be consistent with the production of a disruptive force against the valves, the sequence in question should be regarded as unproved If traumatic rupture of an atrioventricular valve is suspected, the heart should be opened with great care so as to avoid cutting the chordae tendineae.

Injuries of Coronary Arteries and Veins. The functional or vasoconstrictive effects on the coronary arteries of force applied to the heart have been discussed in relation to cardiac commotion. Coronary vascular contusion and laceration remain to be considered

Blunt injury. Although any coronary artery or vein lying in the path of force transmitted from a blunt impact to the

precordium is theoretically capable of being bruised or lacerated, the vascular injury incurred in such circumstances is ordinarily a relatively insignificant feature of the total trauma. The larger epicardial arteries and veins are characteristically less vulnerable to injury by crushing, distorting or displacing forces than the tissue around them. A blunt impact to the chest of such violence as to cause bruising or laceration of a coronary vessel almost invariably produces concomitant myocardial damage of greater import.

In certain special circumstances the effects of trauma may be so sharply localized that vascular contusion is the most significant feature of the injury. Although it might seem plausible that coronary arteries and veins were equally susceptible to such trauma, the significance of venous lesions incurred in this manner is negligible.

Moritz and Atkins (1938) in experiments on dogs exposed the heart and delivered repeated blows over the descending ramus of the left coronary artery (Figure XI-9). The only instances in which recognizable vascular injury was sustained were in those experiments in which gross laceration of the myocardium occurred. Severe myocardial bruising was produced without appreciable damage to the coronary vessels lying directly beneath the site of impact. In unpublished experiments, Moritz observed that it was necessary to crush an artery between the jaws of a clamp in order to produce a localized vascular injury of sufficient intensity to result in thrombosis. Even in such circumstances the production of sufficient trauma to predispose to thrombosis is likely to result in the formation, first, of a false aneurysm due to the escape of blood into the wall of the vessel and, subsequently, to free bleeding into the pericardial sac. Thrombus formation in the lumen of the damaged artery rarely results in occlusion and is characteristically confined to the mural defect, where it organizes as part of the repair reaction.

The difficulties that have been encountered in attempts to produce traumatic coronary thrombosis in animals justify a most critical appraisal of the evidence when it is averred that such a thrombus has occurred in man. The facts (1) that active persons and particularly those engaged in physically arduous occupations frequently sustain thoracic impacts, and (2) that arteriosclerotic heart disease is one of the most common causes of disability and death among the adult population, make it inevitable that many persons develop coronary thrombosis after sustaining some form of thoracic trauma. In an overwhelming majority of such instances the sequence is fortuitous and not indicative of a cause-and-effect relationship. We cannot exclude the possibility that blunt impact may in certain special circumstances produce, in an already diseased artery, sufficient localized injury to precipitate thrombosis. If coronary thrombosis is known to have developed within a few days after a severe precordial impact and if the site of thrombosis corresponds to the path of the transmitted force, the possibility of a cause-and-effect relationship needs to be entertained. If evidence of myocardial contusion or laceration in the vicinity of the vascular lesion is found at postmortem examination of such an individual, the possibility that trauma contributed to the development of thrombosis would be reasonably certain.

Thus, in a death investigated by the author, postmortem examination performed five days after the decedent had sustained a crushing injury of the chest disclosed a transverse fracture of the body of the sternum, hemorrhage throughout the anterior mediastinum, laceration of the parietal pericardium, contusion of the epicardium and myocardium over the

upper anterior portion of the interventricular septum, recent thrombosis of the atherosclerotic proximal segment of the descending ramus of the left coronary and recent infarction of the tip of the left ventricle. Although it was not clear whether the thrombosis had occurred because of direct vascular injury or because of the state of the systemic circulatory stasis and shock which followed the injury, there was no reason to doubt a cause-and-effect relationship between trauma and thrombosis.

THE INDIRECT OR SECONDARY EFFECTS OF PHYSICAL VIOLENCE ON THE HEART

There can be no doubt that a heart already handicapped by a fixed reduction in the patency of its coronary arteries, or by severe myocardial or valvular disease is more likely than is a normal heart to dilate and fail following the imposition of a sudden increase in work load. It is doubtful that a normal myocardium ever sustains permanent injury as the result of exertion or excitement It is a fact, however, that in the presence of severe heart disease, cardiac failure and death may be precipitated by a pressor episode brought on either by violent exertion or by the excitement, rage, fear or pain attending the receipt of injury to any part of the body.

That severe heart disease is often compatible with an apparent state of health is indicated by a report by Moritz and Zamcheck (1946) of the causes of unexpected death of young soldiers (17 to 37 years old) during World War II Although these soldiers had recently passed one or more complete physical examinations in which neither a real nor a potential threat to health was recognized, postmortem examinations disclosed various forms of advanced heart disease of which occlusive coronary atherosclerosis included the largest number. The increased frequency with which the onset of the fatal attack of coronary insufficiency occurred during periods of strenuous physical exertion lends support to the opinion that a pressor episode, whatever its cause may be, is potentially dangerous to an individual whose coronary arteries are too narrow to permit the passage of sufficient blood to the heart

This observation is not in disagreement with Master and associates (1937) who rightfully contend that coronary thrombosis is rarely the result of trauma or exertion. In those soldiers dead of a postexertional attack of acute coronary insufficiency, in whom thrombosis was found, it was apparent in all instances that the thrombus had begun to form before, and not after, the episode that precipitated the fatal collapse. The only circumstance known to the author in which it appears that a pressor episode may be instrumental in precipitating coronary thrombosis is in relation to the kind of thrombosis that results from the rupture of a subintimal hematoma (Paterson, 1939). Spontaneous hemorrhage from capillaries at the base and sides of a coronary atheroma leading to the formation of an expanding subendothelial hematoma which encroaches upon and obstructs the lumen is an occasional cause of acute coronary insufficiency. On several occasions the author has investigated deaths in which it appeared that bleeding into a coronary atheroma had been precipitated by an acute pressor episode and that intraluminal thrombosis had occurred at the site where the hematoma had ruptured through the intimal endothelium.

Another indirect relationship between

trauma and heart failure is that represented by the development of acute myocardial anoxia during a period of posttraumatic circulatory failure. Certainly an important factor in determining the outcome of posttraumatic or surgical shock is the systemic anoxia that develops incident to peripheral circulatory failure. In the presence of atherosclerosis, some parts of the body may suffer more than others during the period of circulatory failure. An occasional complication of, or sequel to, shock in a person suffering from arteriosclerotic heart disease is the development of non-thrombotic myocardial infarction. Thus, disability or death from myocardial insufficiency may result from posttraumatic shock.

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CHAPTER XII

Neoplasms of the Pericardium and Heart

OTTO SAPHIR

Introductory. Primary tumors of the heart are rare, yet Mahaim (1945), who made a careful search of the available literature, recorded 413 primary tumors of the pericardium and heart. Among these, he considered 132 malignant, of which 45 arose from the pericardium and 87 from the myocardium. It must be realized, however, that a number of these reports appeared in the older literature and several are open to question. In view of the apparent rarity of these tumors, it is remarkable that a few actually had been diagnosed correctly some time before the death of the patient. By the use of modern methods of tracing the arterial tree, of catheterization of the right atrium and ventricle, it may be possible eventually

not only to diagnose but actually to locate primary heart tumors exactly. Then perhaps, the surgeon will be able to remove cardiac tumors The following discussion is designed not only to give a classification, an anatomic description and a review of pertinent cases, but also to present such facts as may be important for the clinical recognition of primary cardiac tumors. For practical purposes, certain lesions will be included here which in the strict sense of the word are not true tumors, such as cysts, leukemic infiltrations and Hodgkin's disease.

CLASSIFICATION

Tumors of the heart are usually classified as those found principally in the pericardium, endocardium or myocardium. Such a classification does not imply that the tumors actually arise from these structures, since certain myocardial tumors are believed to arise from misplaced pericardial (mesothelial) structures. In the following discussion, as far as feasible, this classification will be employed.

PRIMARY TUMORS OF THE PERICARDIUM

Tumors arising from the pericardium are rarer than those originating within the myocardium Mahaim was able to collect 84 tumors of the pericardium (Table XII-1), the majority of which were malignant. There were 24 mesotheliomas (coelotheliomas) and 20 sarcomas

TABLE XII-1

Frequency of Various Pericardial Tumors, According to Mahaim (1945)

Tumor	Number
Fibromas	7
Lipomas	3
Angiomas	10
Coelotheliomas (malignant mesotheliomas)	24
Sarcomas	20
Miscellaneous, cysts	19
Unclassified, malignant	1

Mesothelioma

Mesotheliomas, arising from any serous membrane, are very rare; so rare, in fact, that a few authors deny their occurrence. Yet, on rare occasions, every pathologist who has extensive autopsy material at his disposal encounters a tumor obviously arising from a serous membrane. Microscopically, such a tumor may consist of large cells, cuboidal in shape, with eccentrically placed nuclei. Sometimes these cells form pseudoglandular structures, and closely resemble those swollen mesothelial cells so often encountered in chronic inflammation of serous membranes If a carefully conducted postmortem examination excludes a primary tumor elsewhere, one is justified in designating the tumor of the serous membrane as a primary mesothelioma or, according to the French and also the German literature, a coelothelioma

Description. The case report of a malignant mesothelioma by Reals *et al.* (1947) contains a characteristic description. This tumor was found in a 58-year-old white man The pericardial sac was tense, distended, enlarged, dark blue and contained 1000 cc. of bloody fluid The heart weighed 450 grams. The surface of the left ventricle and the entire conus of the heart were studded with hard white masses measuring up to 3 cm. in diameter. The right ventricular surface was almost completely covered with coalescent masses which invaded the heart muscle for a depth of 0.5 cm. Extending from the pericardial cavity along the surface of the pulmonary artery were many small nodules 1 to 3 cm. in diameter. The bronchi were carefully dissected, but no tumor could be found. Metastases were present in the hilar nodes, right pleura,



Figure XII-1 Tumor of pericardium termed endothelioma, but obviously a mesothelioma. The epicardium is exposed Note nodules on both visceral and parietal surfaces (From Dick, J C Endothelioma of the pericardium *J Bact and Path*, 47 43-46, 1938 Reproduced by courtesy of the publishers)

right lung and both kidneys. Microscopically, the neoplasm was highly cellular and there was pronounced pleomorphism. The cells grew in cords with a slight suggestion of whorl-formation, but no definite alveolar arrangement was seen. The nuclei were large with prominent nucleoli, the cytoplasm was acidophilic and finely granular, and mitoses were numerous.

Diagnosis. In the absence of more reliable criteria, the diagnosis of pericardial mesothelioma must rest to a great extent on a process of elimination. Significant in this respect is the report by Robertson (1924) of a neoplasm originally diagnosed as a primary pericardial tumor but subsequently proved to be metastatic from a primary bronchogenic carcinoma. Interesting also are Willis' (1938) conclusions that there are no distinctive histologic criteria for mesotheliomas of serous membranes. In order to render a diagnosis of "mesothelioma" it is necessary to perform a complete postmortem examination and exclude every epithelial structure in the body as a possible source of carcinoma. In regard to histologic findings, Dick (1938) remarked that, in his tumor (Figure XII-1), the elongated acini lined by flattened cells did not resemble primitive vascular channels sufficiently to permit classifying the tumor as a lymphangioendothelioma. He asserted that there was a resemblance to the enlarged lymphatics sometimes seen in inflammatory conditions The likeness of the cellular lining of the more regular acini to the groups of young proliferating pericardial cells (Figures XII-2 and XII-3) found in organizing pericarditis strongly suggested a close genetic relationship and this was further brought out by the irregular alveolar arrangement, the variation in size of the acini and the findings of large irregular intercommunicating channels.

Sarcoma

Steuer and Higley (1935) divided pericardial sarcomas into those limited to the pericardium and those which invade



Figure XII-2. Photomicrograph of tumor shown in Figure 1 Note tumor cells lining connective tissue stroma. (From Dick, J C, *J. Bact. and Path*, 47, 43-46, 1938) Hematoxylin and eosin. X 350, original magnification X 270.

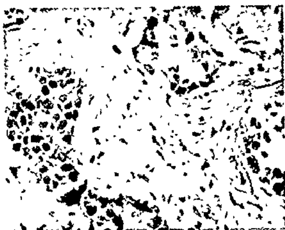


Figure XII-3. Tumor cells similar to those shown in Figure 2, invading the subepicardial connective tissue. (From Dick, J. C, *J Bact and Path*, 47 43-46, 1938) Hematoxylin and eosin X 350, original magnification X 270

the myocardium In their case of sarcoma limited to the pericardium, a large mass within the pericardial sac grossly had the contour of the heart, measured 25 x 19 x 13 cm, was nodular, rubbery in consistency and together with the heart weighed 2450 grams. On section the heart was seen to be entirely surrounded by neoplastic tissue, which extended from the epicardium outward, obliterating the pericardial sac and being intimately attached to the pericardium The tumor was made up of multiple grayish soft nodules which involved the epicardium and compressed the myocardium from without but did not invade it; it also surrounded the pulmonary trunk and ascending thoracic aorta On microscopic section the tumor consisted for the greater part of moderately sized discrete cells with an oval nucleus and a scant rim of acidophilic cytoplasm. The stroma consisted of short, thin, acidophilic fibers which tended to form a reticulated architecture.

Parker and associates (1940) recorded a primary sarcoma of the pericardium which involved the myocardium A large mass filled the middle portion of the mediastinum and a large part of the left side of the thorax and compressed the left lung. The mass appeared to be enclosed within a distended sac and was firm and solid, except for a portion near the base of the heart which was fluctuant. On cross-section it was seen that a yellowish white mass completely encased the heart and distended the pericardial sac. In some regions the neoplastic tissue was firm, in other regions soft and encephaloid. Large and small areas of hemorrhage and firm white bands of fibrous connective tissue extended through the tumor. Although the tumor as a whole seemed rather sharply demarcated from the heart muscle, it had invaded the myocardium in some areas

Bowman (1938) described a primary sarcoma of the pericardium which produced metastases to the lymph nodes in the region of the aorta. A *myxofibrosarcoma* of the pericardium with compression of both atria and of the right ventricle was reported by Schmidt (1948) He believed that this tumor arose on the basis of a faulty development of the primitive mesenchyma

Teratoma

An intrapericardial cystic teratoma, reported by Beck (1942), showed squamous epithelium, sebaceous glands, sweat glands and hair follicles, endometrium, epithelium resembling that of the upper and lower gastrointestinal tract, smooth muscle, fat and lymph follicles. This tumor was recognized clinically and was successfully removed at operation.

Leiomyoma

A leiomyoma of the pericardium was reported by Brandes and associates (1942) in a 19-year-old male They found a bulge of the pericardium over the left atrium and base anteriorly which was dense and

when incised allowed the escape of about 60 ml. of bloody fluid. Microscopic examination of the tumor revealed uniformly appearing elongated cells with long slender nuclei, most of which had blunt ends, and with pale-staining but definitely acidophilic cytoplasm. Hemorrhages were present in some areas Death was unexpected and was probably caused by compression of the atrium by the tumor, the compression having been suddenly increased by hemorrhage. The authors believe that this is the second case of this type on record

Hemangioma

Hemangiomas are very rare (Figure IX-4)



Figure XII-4 Angioma of epicardium (WCGH, 46 A 143)

TUMORS OF ENDOCARDIUM AND MYOCARDIUM

Incidence. The variation in incidence of primary cardiac tumors as encountered at autopsy may be seen from Table XII-2.

TABLE XII-2

Incidence of Primary Cardiac Tumors at Autopsy

Author	*Year of Report*	*Number of Primary Cardiac Tumors*	*Number of Autopsies*	*Remarks*
Thorel	1907	0	3,000	
Bryant	1907	1	2,942	A rhabdomyoma
Karrenstein	1908	0	6,655	
Morris	1933	1	9,000	A round cell sarcoma
Lymburner	1934	4	8,550	
Shelburne	1935	3	12,000	
Pollia and Gogol	1936	154	36,000	Based on all reports in literature up to 1936, these authors considered this incidence to be too high.
Benjamin	1939	12 (03%)	40,000	
Scott and Garvin	1939	0	11,000	
Ravid and Sachs	1943	1	1,888	
Straus and Merliss	1945	0	36,000	
		3	1,550	
Leach	1947	1	648	Autopsies performed on viable fetuses, a tumor, a rhabdomyoma, was found in a stillborn fetus of 6½ months.
		1	6,274	Autopsies included 509 autopsies on viable fetuses and newborn infants, a tumor, a rhabdomyosarcoma, was encountered in a boy of 14 years.
Saphir	Unpublished	2	7,869	Sarcoma reported by Perlstein (1918); myxoma, by Strouse (1938).

Table XII-3 from Mahaim (1945) gives a brief resumé of various types of tumors reported.

TABLE XII-3
Tumors Arising from the Heart (Mahaim, 1945)

Designation of Tumor	*Polypoid Tumors*	*Non-polypoid Tumors*	*Total*
Myxoma	82	23	105
Fibroma	8	29	37
Lipoma	4	10	14
Angioma	4	9	13
Rhabdomyoma	—	60	60
Mesothelioma arising in region of *Tawara's node*	—	5	5
Miscellaneous (cysts and other benign tumors)	—	8	8
Sarcoma	21	66	87
Totals	119	210	329

Age. Cardiac tumors occur at all ages. In Mahaim's series the ages of persons with myxoma of the heart varied from birth after eight months' gestation to 79 years There were five instances in the *first decade, five in the second,* 14 in the third, 12 in the fourth, 16 in the fifth, 13 in the sixth, eight in the seventh, and three in the eighth decade

Sex and Race. There is no appreciable difference in the occurrence of cardiac tumors among the sexes. Since most of *the pertinent literature originated in* European countries, no statement can be *made in regard to the incidence of these* tumors among various races There are, however, isolated reported data of such tumors in the Negro race and in members of the Mongolian race Cardiac tumors are also found in the animal kingdom, and further reference to such occurrence will be made subsequently.

Clinical Features. A few instances of cardiac tumor diagnosed during life have been reported Mahaim stated that of all case reports on cardiac tumors, the correct clinical diagnosis was made 23 times and was suspected in five other patients. However, only eight of these 23 patients disclosed a tumor that was primary in the heart. Woll and Vickery (1947) found two additional metastatic tumors correctly *diagnosed by Hsiung and associates* (1940).

Yater (1931), in his discussion of signs and symptoms of primary heart tumors, stressed the following aspects of diagnosis.

A. Clinical types not suggestive of tumor of the heart:
   1 Absence of symptoms referable to the heart
   2. Symptoms of cardiac embarrassment terminally
   3. Symptoms of congestive heart failure
   4 *Sudden death*
   5. Symptoms suggestive of subacute bacterial endocarditis

B Clinical types suggestive of tumor of the heart:
   1. Heart block
   2 Symptoms other than heart block, referable to location of the tumor
   3 Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
   4. Accumulations of hemorrhagic pericardial and pleural fluid
   5. Suggestive roentgenographic observations

Woll and Vickery remarked that the following findings were suggestive or diagnostic of heart tumor:

1. Unexplained and intractable cardiac failure, which is often the first and final attack
2 Unexplained and sometimes inconstant changes in cardiac rhythm, sounds and size, as physical, roentgeno- electrocardiographic —

3. Development of a hemorrhagic pericardial effusion. (The presence of neoplastic cells in the fluid may confirm the diagnosis.)
4. Unexpected signs of obstruction of the cardiac blood flow or of the blood flow of the major thoracic vessels
5. A specimen removed in arterial embolectomy which is shown on microscopic examination to be derived from a tumor of the heart

Respiratory difficulty is a striking feature in patients with atrial tumors. Field and associates (1945) remarked that the most characteristic feature of such tumors is the inability to ascribe a satisfactory etiologic cause for the obvious signs of organic heart disease It is only by careful observation, frequent clinical examinations and accurate follow-up of patients, with this condition in mind, that more definite criteria for early diagnosis may be assembled. There is general agreement that cardiac tumors would be recognized more often if the clinician considered them in the differential diagnosis of a relevant cardiac condition.

Beck (1942) reported a remarkable case in which a cardiac tumor (a cyst) not only was diagnosed clinically but also was successfully removed and the patient lived, even though most of the "tumor" prior to operation had been embedded in the myocardium. The electrocardiographic changes present before operation eventually disappeared entirely and the patient appeared to be cured The "tumor" proved to be not a true neoplasm but a cyst that had calcified walls and contained material having the consistency of packed clay. This was apparently the first time that a benign cyst or tumor of the heart was recognized clinically and removed successfully.

Myxoma

Nature of Lesion. Endocardial tumors are recorded more frequently than all other primary heart tumors. They arise in the region either of the mural or of the valvular endocardium. Depending upon the point of view of the observer, they are classified as true tumors or pseudo-tumors. In the older literature (see Thorel, 1907), these lesions were almost invariably classified as true tumors. Thorel, however, stressed that not a single instance reported up to that time could possibly be classified as a true unquestionable myxoma but must, in the final analysis, be regarded as an organized thrombus. Husten (1923) also studied critically all the available relevant instances and interpreted the so-called myxomas of the heart as thrombi in various stages of organization In Husten's series of 86 myxomas, the left atrium was involved 71 times, the right atrium nine times, the right ventricle three times, and the left ventricle three times. Within the left atrium the tumor arose from the region of the foramen ovale in 45 instances; the pulmonary veins and the left auricular appendage were the other preferred sites of origin. Seventeen of the 71 instances of tumors in the left atrium did not disclose sufficient data to make them adaptable to analysis. Husten classified these lesions as (1) thrombi, (2) those in which the diagnosis was difficult, being either thrombi or myxomas, and (3) those which fulfilled certain criteria of myxomas. In studying the location of these lesions within the left atrium, he noted that each lesion involved the three regions of the left atrium just mentioned (fossa ovalis, region of pulmonary veins, auricular appendage) in about equal frequency. He therefore concluded that the nature of these three lesions is also most likely identical, *i.e.*, they represent the end-results of organized thrombi. Husten's point of view

was opposed by Ribbert (1915) who stated that often the size of these lesions is much more in favor of their neoplastic nature, as is their lobulated and "villous" appearance. Fabris (1923) listed the points for distinguishing between thrombi and myxomas, according to Table XII-4.

TABLE XII-4

Distinguishing Features in Diagnosis of Myxoma and Organized Thrombi
(Slightly Modified from Fabris, 1923)

Feature	*Myxoma*	*Organized Thrombus*
Preferred location	Mitral valve and foramen ovale	Atria
Gross appearance	Thick cauliflower-like mass	Contour more regular
Surface	Villous, transparent	Granular, opaque
Base	Thin pedicle	
Consistency	Soft, gelatinous	Firm
Endocardial covering	Continuous	At junction of implantation
Cells, number, arrangement and type	*Few cells with cytoplasmic processes,* in colorless stroma. Cells mainly stellate, isolated or in groups or forming syncytia. Cells embryonic.	*Stratified, several layers. External por*tion composed of granulation tissue with abundant extravasation of red blood cells. Foci of round inflammatory cells.
Special features		
Hemosiderin	Absent	Abundant
Mucin	Present	Absent
Elastic fibers	In vicinity of vessels	Absent
Features in common	Localization in valves, accumulation of bacteria, presence of vessels.	

Mahaim (1945) emphasized that myxomas often contain blood vessels and may, therefore, disclose hemorrhages and hemosiderin, that fibrin may be found on their free surfaces, and that the microscopic aspects may not aid in the differential diagnosis. He stated that a number of pathologists, after having studied the evidence for and against the neoplastic origin of these structures, admitted their inability to distinguish myxomas from the end-stages of certain organized thrombi. In certain publications, therefore, the histologic diagnosis is left open. Yet, from his personal experience, Mahaim concluded that there exist localized proliferations of mucous tissue within the endocardium which merit the classification of myxoma. An organized thrombus may, as a result of regressive changes, simulate a myxoma. On the other hand, trauma may be responsible for hemorrhage within a myxoma. Mahaim collected from the literature reports of 105 myxomas, of which 82 were pedunculated and 23 sessile. One argument often used against the thrombotic origin of myxomas is that the latter are extremely rare in the ventricles. According to Mahaim, only 20 such instances are recorded in the literature. If so-called true myxomas of the atria were organized thrombi one would expect to find in the ventricles, where thrombi are very common, many more lesions comparable to myxomas of the atria. It is, therefore, argued that myxomas and thrombi have nothing in common and are two different lesions. Mahaim also found that myxomas are encountered much more frequently in the left atrium than in the right. Of the 82 pedunculated myxomas there were 68 in the left atrium and only 14 in the right.

"Polyp." In the French literature the term "polyp" is often used both in the sense of a pedunculated neoplasm and of a pedunculated thrombus, making it rather difficult for a reviewer to find the exact meaning of "polyp" in a particular instance. Since "polyp" means a pedunculated mass or neoplasm arising from a mucous membrane, the term should never be applied to a cardiac lesion.

Gross Appearances. Yater (1931) described the gross and microscopic appear-



Figure XII-5 Intra-atrial tumor reported as myxoma of the left atrium (From Hamilton-Paterson, J L, and Castleden, L I M Intracardiac tumours, *Brit Heart J*, 4 103-114, 1942 Reproduced by courtesy of the publishers)

ances of myxomas They range in size from "a pea to a hen's egg or a medium-sized apple" (0 4 to 8 cm in largest diameter). They may be smooth and rounded, lumpy or polypoid and villous, the surface being smooth and glistening, as a rule, and the appearance gelatinous (Figure XII-5). They are usually pale, yellow, bluish gray or yellowish brown, often with hemorrhagic areas on the surface, and sometimes partly covered with fibrin The consistency is more or less elastic and on cut section, they are gelatinous and often hemorrhagic. They are usually attached by a short stalk and are entirely intracardiac.

Microscopic Features. The tumor is covered with the normal endothelium of the endocardium. The groundwork is an amorphous, finely granular or finely fibrillar material which may or may not stain as mucin. Cells of different varieties are seen, varying in number in different parts of the same mass; often they are relatively few compared to the total amount of myxoma tissue. In many there are large stellate cells typical of myxomatous tissue. In some there are also cells that are large and multinucleated, or cells that are fusiform, while inflammatory elements such as lymphocytes and plasma cells are often seen. Blood vessels are usually present, sometimes numerous, but often scanty, usually of a delicate structure, and appearing as mere capillaries with endothelial walls. Small hemorrhages and scattered erythrocytes are commonly present, together with pigments consisting of hemosiderin and hematoidin. Connective tissue fibers and often elastic fibers are found.

There are also on record cases reported as "malignant" myxomas (Ringertz, 1942, Fenster, 1933). A critical review of Ringertz' report suggests the possibility that the original lesion was a thrombus which gave rise to multiple emboli, while Fenster's tumor should be classified as either a spindle cell sarcoma or, perhaps, a neurogenic sarcoma.

Evaluation of Myxoma. From the foregoing it may be seen how difficult it is to differentiate between myxomas and end-stages of organized thrombi. One is certainly justified in questioning the existence of true myxomas of the heart. Prichard (1951) concluded that myxomas form a uniform group of tumors, occurring in a definite location in the heart and having a characteristic gross and microscopic appearance. He reported two instances of myxoma and pointed out that the bulk of evidence indicates that they are true neoplasms. It seems obvious that a more conservative point of view should be adopted and that any sessile or pedunculated lesion which could perhaps be interpreted as myxoma should be regarded as the end-stage of an organized thrombus unless definitely proven otherwise. One cannot say that such definite proof will be forthcoming in the future. In a study, entitled *Intracardiac Tumors*, Hamilton-

Paterson and Castleden (1942) list such a lesion of the left atrium as "pseudomyxoma."

The difficulty of distinguishing between myxoma and organized thrombus may be inferred from Weinstein and Arata's report (1949). They described a neoplastic lesion in the left atrium which, they believed, had produced mitral stenosis and insufficiency. The tumor was interpreted as a myxoma. The gross picture of the heart, however, shows definite thickening of the chordae tendineae of the mitral valve. Also the presence of an embolus in one of the femoral arteries would indicate that the "myxoma" was probably a thrombus. In the report of Orr (1942), who described a polypoid tumor of the left atrium of the heart, a number of endothelial structures were present microscopically, which led the author to conclude that this was essentially an endothelioma. A picture of the gross specimen is included showing the "tumor" and the mitral valve, and the chordae tendineae are described as thickened and shortened. Thus, it seems that the mitral valve was the seat of an old endocarditis, which throws doubt on the neoplastic nature of this lesion.

Clinical Significance. So-called myxomas are often incidental autopsy findings, unsuspected clinically. Yater (1931) remarked that many of the myxomas are interesting because of their size, structure and pedunculated nature, which allows them to plug up an orifice of the heart, usually the mitral. Straus and Merliss (1945) stated that a large tumor of an atrium with a ball-valve action on either the mitral or the tricuspid ring, producing murmurs affected by a shift in the position of the body, should certainly be susceptible to clinical diagnosis. And yet, in no case of benign tumor of this type has the diagnosis been made before death. Unexpected death may apparently result from sudden occlusion of either the mitral or the tricuspid orifice by an intracavitary pedunculated tumor (Yater).

Surgical Removal. Concerning the possibility of removing some of these myxomatous masses surgically, Beck (1942) stated that it seems that some of the soft myxomas arising from the endocardium could be so removed. It might be possible to remove them in much the same way as a neurosurgeon removes a soft glioma of the brain by means of strong suction. It would seem possible to insert a glass suction tube into the atrium for this purpose. He also thought it might even be possible to open the atrium and remove the mass. *Coulter (1950)* likewise drew attention to the possibility that such tumors may be removed surgically, if recognized during life.

Myxomas of Heart Valves. Myxomas arising from the heart valves are also the subject of much controversy. Ribbert (1924) emphasized that myxomas of the valves are almost invariably larger than thrombi and it seems difficult to believe that complete organization of thrombi could materialize from the valvular endocardium. Organization of larger thrombi usually results in an encapsulation with regeneration of the endocardial cells, the center of the thrombus still being liquid or becoming liquified secondarily. However, it does not seem likely that the center of a large thrombus may ever be completely replaced by fibrous tissue with secondary myxomatous degeneration so as to simulate a myxoma in which the myxomatous tissue is spread out diffusely. Ribbert also remarked that an organized thrombus would eventually lead to scar tissue within the adjacent valvular tissue, as seen in instances of healed thrombo-endocarditis.

Three types of so-called occlusive myxomas ("polyps") of the mitral valve are recognized by Mahaim (1945):

1. Occlusive pure mitral "polyps" with

clinical signs of stenosis of mitral orifice and without mitral lesions at autopsy
2. Occlusive pure mitral "polyps" without signs of stenosis of mitral orifice, with or without systolic murmurs of functional mitral insufficiency
3. Occlusive mixed mitral "polyps" with associated mitral lesions. Clinical signs of stenosis of mitral orifice are constant but often masked by severe arrhythmia

Jaleski's (1934) report of a so-called myxoma of the tricuspid valve is interesting insofar as justifiable criticism may be presented in regard to the classification of this lesion. His patient was a 62-year-old colored woman who suddenly collapsed five days after a cataract extraction and died the next day On the middle portion of the anterior cusp of the tricuspid valve about 5 mm from its edge was a small spherical papillary mass, measuring 6 mm. in diameter and projecting 4 mm above the surface of the valve to which it was attached by a wide pedicle. Its surface was finely nodular and it had a translucent gelatinous appearance Stained with hematoxylin and eosin the mass was entirely lined by endothelium and its matrix was pink. The papillae contained only a few cells and there were no blood vessels present; the pedicle, on the other hand, contained many stellate and spindle-shaped cells which had fine processes extending from them into the fine fibrillar groundwork present throughout the lesion. Thus the gross and microscopic description of this pertinent lesion, reported as myxoma of the heart valve, would suggest that this is indeed a true tumor of the heart. However, a gross picture of the right ventricle, included to show the tumor, also shows evidence of old endocarditis, which immediately raises doubt as to the neoplastic nature of the lesion.

Other Terms for Myxoma. In this connection it may be mentioned that Warthin (1916) thought that some of the so-called myxomas of the heart represented gummas, and for these he coined the term "myxogummas." Some of the more recent reports of these small valvular lesions also cast doubt as to their true nature. Thus, Engel (1932) spoke of a "peculiar fibromyxomatous hyperplasia" of the mitral valve He regarded this lesion as a transition between hyperplasia and tumor.

"Fetal Endocarditis." In reviewing a number of reports of myxoma of the heart one is reminded of the small myxomatous lesions which are encountered not rarely on various valves of newborns or stillborns and which in the older literature have been called "fetal endocarditis" Gross (1941) has shown that these structures are remnants of the jelly-like material which makes up the original endocardial cushions It is conceivable that such structures may persist and eventually become organized, giving rise to either so-called valvular myxomas or fibromas.

Excrescences of Lambl. Lambl in 1856 described small villous, comb- or tassel-shaped excrescences situated principally on the free borders of the valves and rarely involving the leaflets on the line of closure. Kirch (1927) stated that Lambl's excrescences are definitely not tumors, but should be considered, according to Ribbert (1924), to be the result either of organization of thrombi or of proliferation of the subendocardial connective tissue. Kirch noted Lambl's excrescences often close to the corpus arantii. Gunzel (1933) asserted that Lambl's excrescences of the aortic valve are much more common than is usually assumed. He maintained that with increasing age they are seen more frequently. They are not the result of organizing thrombi and they do not constitute products of inflammation, since they are always avascular and free from cellular infiltra-

tion. He believed that because of the continuous, perhaps abnormal, systolic and diastolic pressure, a tear of the lining endocardium may cause the previously stretched and broken collagenous or elastic fibers to project over the endocardial surface. Eventually these fibers become endothelialized again. Magarey (1949) examined the mitral valve in 280 autopsies He found Lambl's excrescences in 85 per cent and determined that their incidence increased with age He believed that they are a manifestation of wear-and-tear and part of the normal aging process of the valve. They are the result of organization of partially attached fibrin on the surface of the valve. This process occurs repeatedly and leads to gradual thickening of the cusps.

OTHER TUMORS OF HEART

Fibroma. Fibromas in the heart have also been recorded. These obviously arise from the subendothelial connective tissue of endocardium (Figure XII-6), almost all the reported fibromas being located on a heart valve. Mahaim (1945) mentioned a number of instances of fibromas of the various valves as collected from the literature. It was sometimes difficult to decide from the available literature whether the lesion in question was a fibroma, myxofibroma, myxoma, fibrohemangioma, or an excrescence of Lambl. Such lesions were found on the mitral valve three times, on the aortic valve eight times, on the pulmonic valve seven times, and on the tricuspid valve twice Kulka (1949) reported an intramural fibroma in the left ventricle of an eight-month-old infant who had died unexpectedly.

A papillary branching fibroma of the tricuspid valve was reported by Branch (1931) The tumor consisted of papillary stalks which were composed of a single or compound core of dense collagenous fibrils surrounded by loose connective tissue, outside of which was a layer of homogeneous material covered by endothelium. The tumor contained no blood vessels. Hertzog (1936) also described a fibroma of the middle cusp of the aortic valve. He stated that there was no evidence of old endocarditis Hertzog remarked that his tumor was similar histologically to some of the reported cases of myxoma of the heart valves. However, myxomatous tissue could not be demonstrated.

Roth and Spain (1952) described a tumor which they believed to be a primary granular cell myoblastoma of the left atrium. It was firm, covered by pericardium and fixed to the subepicardial tissue and myocardium. The cells were fairly uniform in size and shape, infiltrated the interstitial tissue, and contained an abundant cytoplasm which appeared to be granular or clumped

Lipoma. Lipomas of the heart are extremely rare. Mahaim (1945) recorded 14 such tumors.

A typical lipoma of the heart was encountered by me in the right atrium of a 50-year-old woman who died suddenly The tumor was bright yellow, measured 3 cm. in greatest diameters, was covered by epicardium and bulged into the right atrium. It seemed to be well circumscribed grossly but microscopically was not circumscribed and had no evidence of a capsule; a few atrophic muscle fibers were scattered throughout the tumor. It was apparent that the fatty tissue had infiltrated the myocardium, replacing the muscle fibers. The same changes are found in fatty infiltration of the myocardium (Saphir and Corrigan, 1933), in which the subepicardial fatty tissue also extends into the adjacent myocardium, produces atro-



Figure XII-6 Pedunculated fibroma X 190 (Courtesy of Armed Forces Institute of Pathology, Acc. 38558)

phy of the fibers and, like a malignant tumor, eventually replaces the muscle fibers. Thus, the question must be raised whether these lipomas of the heart represent circumscribed areas of fatty infiltration or are true benign tumors which grow by expansion and are not surrounded by a capsule.

Angioma. Mahaim asserted that pure angiomas of the heart are very rare, only 13 such tumors having come to his attention. They should be clearly distinguished from varicose dilatations (see page 893) and they may be associated with proliferation of endothelial lining cells.

A small tumor of this type was found by Schuster (1914) in a newborn infant on one of the papillary muscles of the right ventricle close to the attachment of one of the chordae tendineae. This nodule measured 2.5 × 1.5 cm. in greatest dimensions. Microscopically, it consisted of two parts, one part was interpreted as the end-result of a circumscribed inflammation of

the endocardium, and the other part, as a true tumor, a cavernous hemangioma. The author denied the existence of any relation between the circumscribed inflammation (endocarditis) and the tumor. A review of this report immediately raises the question as to whether the structure described as cavernous hemangioma is identical with the so-called blood cysts found on the heart valves in the newborn (see page 903).

Angio-Reticuloma. Angiomas should not be confused with true benign tumors of the angio-reticuloma type of the endocardium which Mahaim (1945) believes are similar to those occurring in the cerebellum and spinal cord, as described by Cushing and Bailey (1928). It may be of interest in this respect to mention the description by Nicod, in a woman of 74, of a tumor of the endocardium located in the left atrium near the foramen ovale. It showed microscopically angiomatous and reticuloendotheliomatous structures. Mahaim speculated on the possible changes which might occur in such a tumor developing in a young person, if it was subjected for a long period of time to the trauma of the blood stream and of cardiac contraction. He believed that changes might occur in such a tumor which would simulate the appearances of both a thrombus and a myxoma He directed that attention should be paid to the so-called angioreticuloma of Nicod (1945) and asserted that many of the polypous tumors of the atrium whose origin at the present time is under dispute could perhaps be traced to these angio-reticulomas.

Malignant Hemangioendothelioma. A primary malignant hemangioendothelioma of the heart with widespread metastases in the liver and esophagus was described by Hewer and Kemp (1936) Gross and Englehart (1937) described another primary hemangioendothelioma of the heart. This diffusely infiltrated the wall of the left atrium and had grown into thrombi which were adherent to the left atrial wall, the mitral valve and the left ventricular wall. There was no evidence of tumor embolism or metastasis outside the heart Stout (1943) contended that a tumor should be considered hemangioendothelioma only if it contained, first, atypical endothelial cells in excess of the number required to line the vessels with a simple endothelial membrane and, secondly, vascular tubes with a delicate framework of reticulin fibers and a pronounced tendency of their lumina to anastomose.

Glassey and Massey (1950) also reported a primary hemangioendothelial sarcoma of the heart, this had involved the pericardium and endocardium They believed their tumor to be the 349th recorded primary cardiac neoplasm

It is open to question whether or not some of these tumors can be classified under the term *Kaposi's tumor* (sarcoma idiopathicum hemorrhagicum) in which there are multiple vascular foci of tumor formation Rabson (1938) suggested that there are indications that hemangioendothelioma and Kaposi's disease may have certain elements in common Though Ewing (1940) does not mention the heart specifically, he stated that in Kaposi's disease every organ of the body has been found involved at autopsy.

Rhabdomyoma (Nodular Glycogenic Degeneration)

Rhabdomyomas are described involving the heart either diffusely or in the form of isolated (Figure XII-7) or multiple nodules. An example of the nodular form is given in the excellent and detailed description of this lesion by Farber (1931) who reported its occurrence in a six-month-old female infant in association with tuberous sclerosis of the brain The heart was enlarged, weighing 90 grams. A number of masses were found bulging into the right



Figure XII-6 Pedunculated fibroma X 190 (Courtesy of Armed Forces Institute of Pathology, Acc 35558)

phy of the fibers and, like a malignant tumor, eventually replaces the muscle fibers. Thus, the question must be raised whether these lipomas of the heart represent circumscribed areas of fatty infiltration or are true benign tumors which grow by expansion and are not surrounded by a capsule.

Angioma. Mahaim asserted that pure angiomas of the heart are very rare, only 13 such tumors having come to his attention They should be clearly distinguished from varicose dilatations (see page 893) and they may be associated with proliferation of endothelial lining cells.

A small tumor of this type was found by Schuster (1914) in a newborn infant on one of the papillary muscles of the right ventricle close to the attachment of one of the chordae tendineae. This nodule measured 2.5 × 1 5 cm. in greatest dimensions. Microscopically, it consisted of two parts; one part was interpreted as the end-result of a circumscribed inflammation of



Figure XII-8B Nodular glycogenic infiltration Same case as Figure XII-7
X 400

atrium and right ventricle which varied in size from 0.9 × 0.8 × 0.2 cm to 1.3 × 0.9 × 0.8 cm. in *greatest dimensions* One mass obstructed the orifice of the tricuspid valve. A number of small nodular excrescences were also present between the papillary muscles near the apex of the right ventricle. The left atrium was not involved but a few small nodules, each approximately 1 mm in diameter, were scattered in the myocardium of the left ventricle On section the nodules were yellowish or grayish yellow and moderately firm, and the cut surfaces smooth and slightly bulging There was a suggestion of concentric arrangement near the line of gradual merging with normal-appearing myocardium.

Microscopic Features. The following microscopic description is taken from Farber Examination of tissue fixed with Zenker's solution disclosed large vacuolated spaces of round or oval shape and irregular size, giving the sections a loose, spongy appearance (Figures XII-8A and B) Numerous heavy connective tissue trabeculae, containing blood vessels, coursed through the lesion, giving off finer and more delicate branches which ramified among the large vacuolated spaces Thick protoplasmic walls surrounded the spaces, and between them in places was a thin, delicate connective tissue reticulum. Some of the spaces were empty, while within other spaces were cells with many processes. There was great variation in the size and shape of these cells, depending in part on the size of the spaces in which the cells were located. The processes ran from the central protoplasmic mass in bizarre and irregular fashion. Sometimes they anastomosed richly and divided into finer elements until they merged with the wall. Often the proc-



Figure XII-9 So-called rhabdomyoma Note "spider cell" Pollak's modification of trichrome stain X 500, original magnification X 365 (From Pratt-Thomas, H R Tuberous sclerosis with congenital tumors of heart and kidney, *Am J Path*, 23 189-199, 1947 Courtesy of *American Journal of Pathology*)

esses were short, plump, and few in number, in places failing to merge with the wall On close examination these processes were transversely striated by rows of delicate granules. With suitable stains these granules stood out clearly, and the processes as well as the wall of the spaces showed numerous definite cross-striations.

The cells generally had but one nucleus, occasionally two, and rarely three or four nuclei. Sometimes clear spaces surrounded the nuclei and in such cases the processes were generally short and plump. Each nucleus usually contained a single nucleolus. Occasional evidence of direct division was noted and no mitotic figures were seen. Sections stained with Best's method showed large amounts of glycogen in the

them are apparently most characteristic and their presence is emphasized in most reports. These cells are often referred to as "spider cells" (Figure XII-9). The content of the vacuolated spaces is glycogen. The tissue between the spaces is sometimes composed of large polygonal branching cells having finely granular and eosinophilic cytoplasm (Labate, 1939). Steinbiss (1923) stated that some of these lesions, after degeneration, may go on to scar tissue formation.

Location of Nodules. The tumor nodules may be present in both atria (Olsen and Cooper, 1941) or in the ventricles and atria (Mitani, 1934) or in the ventricles alone (Steinbiss). They may be found close to the bundle of His or away from it.

Frequency. Rhabdomyomas of the heart are very rare. Farber (1931) stated that, exclusive of his report, only 33 undoubted cases of the multiple type and eight of the single type had been reported Labate in 1939 added eight new cases which he collected from the literature and one which he had observed himself Olsen and Cooper (1941) recorded an instance with multiple nodules in the heart. Batchelor and Maun in 1945 collected reports of 62 cases, 10 of which had appeared in the American literature, and they added another example. Kidder (1950) found a total of 69 such tumors. In regard to the apparent rarity of these lesions, Steinbiss stated that rhabdomyomas are often associated with tuberous sclerosis, these patients do not necessarily die in infancy but, because of concomitant mental disturbances, are later admitted to institutions for the care of the feeble-minded He pointed out that autopsies in mental institutions are either not performed or are limited to an examination of the brain, and stated that if more complete autopsies were performed more rhabdomyomas would be found. Steinbiss found 6 rhabdomyomas among 31 patients with tuberous sclerosis, dying in mental institutions. Kirch (1927) also asserted that rhabdomyomas are not as rare as generally believed.

Age and Race. In the cases reviewed by Farber, 12 of the patients with rhabdomyomas were over three years old, the oldest being 35. Table XII-5 from Batchelor and Maun's (1945) report is included to give the age of the patients with rhabdomyomas of the heart (63 patients)

TABLE XII-5
Age of Patients with Rhabdomyoma of Heart
(From Batchelor and Maun, 1945)

Newborn	15
Under 1 year	18
1 to 3 years	9
3 to 15 years	12
Over 15 years	7
Age not given	2
Total	63

Hueper in 1935 reported the first instance of the occurrence of this lesion in the Negro. Pratt-Thomas in 1947 recorded another such lesion in a premature Negro infant.

Clinical Features. Kirch (1927) pointed out that rhabdomyomas have never been diagnosed clinically. In a number of instances, symptoms referable to associated tuberous sclerosis of the brain could be elicited (Steinbiss, 1923). Wegman and Egbert (1935) reported a patient in whom cardiac arrhythmia was detected clinically. In the reports reviewed by Batchelor and Maun cyanosis was listed as a frequent symptom, especially in newborn infants and in those who died unexpectedly Monckeberg (1924) mentioned that in several patients evidence was noted of stenosis of the orifice of the pulmonic valve, produced by tumor nodules within the conus pulmonalis In practically all of the reported instances, however, the finding of rhabdomyomas was unexpected.

Association of Tuberous Sclerosis and Other Lesions. Labate (1939) stated that in 57 per cent of the 29 patients in the cases reviewed by him, tuberous sclerosis of the brain was also found. In Batchelor and Maun's (1945) series the incidence of tuberous sclerosis was 50 per cent. They asserted that the frequency of association of the two lesions is actually much higher. Various tumors of the glioma group have also been found associated with tuberous sclerosis Kidney tumors, angiomyosarcomas, angiolipomas, cysts, nests of embryonal tissues, various malformations, and adenomas, especially sebaceous adenomas, are also frequently encountered in patients with congenital rhabdomyomas of the heart.

Occurrence in Animals. It is interesting that similar lesions in the heart have been observed in animals also. Hieronymi and Kukla (1921) described a number of smaller and larger nodules in the heart of a four-month-old pig Also Joest (1923) and, later, Clausen (1938) each found a solitary rhabdomyoma in the heart of a pig. Pires and Mucciolo (1939) reported such a tumor in a cow and Hueper (1941) described multiple rhabdomyomatous nodules in the heart of a guinea pig, the heart weighing 245 grams.

Origin of Rhabdomyomas. There are various views regarding the origin of rhabdomyomas of the heart The fact that the lesion is characterized by many large seemingly empty spaces gave rise to various speculations that these may be regarded as lymph spaces, artefacts, or interstitially located spaces similar to those found between anastomosing cells in the hearts of human embryos.

However, Wolbach (1907) by the use of the phosphotungstic acid and hematoxylin stain, offered conclusive evidence that these spaces were located within the muscle fibers. That these empty spaces within the muscle fibers might represent dissolved glycogen was first suggested by Seiffert (1901) in a report before the German Pathologic Society and this opinion was supported by Marchand *in a discussion of* Seiffert's communication. Askanazy, in the same discussion, stated that he had actually found glycogen in a rhabdomyoma

which had come under his observation. Rehder (1914) clearly demonstrated the presence of glycogen in "tumor" cells, and in most of the lesions recorded later, glycogen was demonstrable. Because of the morphologic resemblance of Purkinje cells and the elements of the rhabdomyoma, and because of the presence of much glycogen in both the Purkinje fibers and the fibers within the rhabdomyoma, the conclusion was drawn by a number of investigators that the rhabdomyomas may arise from the Purkinje cells (see Farber, 1931). However, it is clear that these "tumors" were often found, as Steinbiss (1923) remarked, in regions of the heart away from the conducting fibers He also stated that disturbances of conduction during life had never been noted.

Steinbiss (1923) thought that both rhabdomyomas and tuberous sclerosis might be explained on the assumption of an "excess" in the cardiac and brain Anlagen. Ribbert (1915) emphasized a local disturbance somewhere during the growth of the heart muscle. He thought that muscle elements in an early stage of development were thus separated from the rest of the myocardium and grew independently. He, therefore, classified rhabdomyomas as choristomas. Rehder, however, regarded rhabdomyomas as simple malformations of muscle structures and grouped them among hamartomas. Both authors emphasized that because of the multiplicity of the lesions, their appearance, and their lack of tendency to grow, they should not be classified as tumors. Both Monckeberg (1924) and later Kirch (1927), in their respective monographs, after reviewing the available material concluded that rhabdomyomas should not be regarded as true tumors. As late as 1942, Hamilton-Paterson and Castleden classified this lesion among benign congenital tumors arising from developing myocardial elements (congenital rhabdomyoma, dysontogenetic rhabdomyoma, hamartoma). Hertzog (1949), who described diffuse rhabdomyomatosis of the heart in a two-month-old infant, also interpreted this tumor as a hamartoma.

The modern concept of rhabdomyoma can be traced to von Gierke's first publication of his "hepatonephromegalia glycogenica" in 1929. In it he also mentioned an instance of a diffusely enlarged heart in a child in whom the enlargement was the result of glycogen infiltration. Putschar (1932), three years later, published the first detailed report of congenital glycogen infiltration of the heart in a four-month-old child. It is interesting that just ten years earlier Schmincke (1922) had recorded an instance of congenital hypertrophy of the heart, the result of "diffuse rhabdomyomas" with much glycogen obvious within the muscle fibers, this was so characteristic of glycogenic infiltration that Pompe in 1933 referred to this case as being typical of von Gierke's glycogen-storage disease. Pompe also ventured the opinion that a number of other instances reported as idiopathic hypertrophy of the heart probably are examples of von Gierke's disease Curiously enough, as early as 1864, Virchow thought that perhaps idiopathic hypertrophy of the heart could be explained by a diffuse rhabdomyoma of the heart.

Humphreys and Kato in 1934, while studying glycogen-storage disease, suggested that in view of Pompe's observations it might be well to examine critically the rare cardiac rhabdomyomas to see if they represent localized or diffuse glycogen disease (cardiomegalic glycogen-storage disease). Olsen and Cooper (1941) stated that, because of poor terminology, nodular glycogen tumors have been confused with rhabdomyomas, which they classified as true neoplasms. For this reason they advised alteration of the terminology from congenital rhabdomyoma or rhabdomyomatosis to a more suitable and

distinctive term, *congenital nodular glycogenic degeneration of the myocardium* The latter nomenclature conforms with the objective findings of the disease without suggesting a neoplastic origin or implying an exact knowledge of the etiology It seems that these authors classify all congential "tumors" of this type as localized lesions of glycogen-storage disease, but do not deny that true rhabdomyomas exist in the heart, perhaps without the presence of much glycogen within the fibers. Batchelor and Maun (1945), apparently in partial agreement with Olsen and Cooper (1941), suggested the term "congenital nodular glycogenic tumors of the heart" for their case report. Leach (1947) in the summary of his report spoke of rhabdomyoma or congenital nodular glycogenic tumor Sussman and Stasney (1950) believed that congenital nodular tumors of the heart should not be classified as neoplasms, but as hamartomas or tumor-like malformations consisting of misplaced striated muscle tissue with glycogen deposition These authors reported the occurrence of a lesion in a patient who had an arrhythmia. Prichard (1951) regarded rhabdomyomas of the heart as hamartomatous nodules which may regress He believed that they represent focal arrest in maturation of the cardiac muscle. However, he did not believe that the existence of diffuse true rhabdomyomas has been proved, and stated that reported examples are probably manifestations of localized glycogen storage disease.

Hueper (1941) pointed out that the glycogen contained in the primitive muscle cells of rhabdomyomas is much more soluble in the ordinary fixatives than the glycogen stored in the various organ cells, such as liver and heart, in glycogen-storage disease. This difference is brought out strikingly by the fact that glycogen in the cells of rhabdomyomas has been demonstrated only very rarely, the glycogen being removed from these cells by fixation in aqueous media before the proper staining procedures are applied, while the glycogen present in the tissues of von Gierke's disease has been demonstrated by chemical and staining methods after having been in fixing fluids for weeks or months. In the latter instance, the glycogen is not only markedly resistant to postmortem hydrolysis but it is also much less soluble in watery agents than ordinary glycogen, including that contained in rhabdomyoma cells. This histochemical property in conjunction with the demonstration of "spider cells" and various myofibrillar evolutionary manifestations in the primitive myocardial cells may help in the future in distinguishing between rhabdomyomatous lesions and myocardial tissue changes associated with von Gierke's glycogen-storage disease.

Summary. There exists in the myocardium a lesion, either localized or widespread, which in the earlier literature was classified as congenital rhabdomyoma. It was soon recognized that this lesion is not encapsulated, that it merges imperceptibly with the surrounding healthy myocardium, that morphologic evidence of malignancy is never encountered and that metastases are unknown It seems to grow only at the same rate as the adjacent normal muscle structure. Because of its histologic features and because of associated lesions, especially tuberous sclerosis of the brain, the cardiac nodules were early considered to be muscle malformations and were classified as hamartomas. The rich glycogen content of the fibers of rhabdomyomas has often been emphasized, and early investigators, attracted by the morphologic resemblance of the "empty" fibers in the nodules to the fibers of the bundle of His and by the fact that both are rich in glycogen, thought that rhabdomyomas may arise from the fibers of the conducting system When glycogen-storage disease be-

came known, it was soon suggested that these congenital rhabdomyomas were expressions of this disease and terms like "nodular glycogenic degeneration of the heart" and "glycogenic tumors of the heart" were coined. At present the etiology of congenital rhabdomyomas is still unsettled but it is generally agreed that they are not true tumors. Are they hamartomas or do they represent localized manifestations of glycogen-storage disease (von Gierke's disease)? The difference in the chemical behavior of the glycogen in von Gierke's disease from that in the nodules, as Hueper has emphasized, are not sufficiently distinctive to be used as means of distinguishing the two lesions. From the evidence at hand, it seems that true rhabdomyomas (true tumors) of the heart, if they exist at all, are extremely rare. Most of the reported instances are examples of localized glycogen-storage disease with or without the simultaneous presence of various hamartomas, on the basis of which, as in the brain, true tumors may develop

Sarcoma Arising in the Myocardium

Malignant primary tumors of the myocardium are also very rare.

Perlstein in 1918 reviewed this subject, found only 30 which he regarded as sarcomas, and added an additional one. Mahaim (1945) accepted 87 tumors as true sarcomas but a critical review of these disclosed that apparently not all are primary tumors. Thus Guttmann's (1889) so-called primary melanoma is obviously a secondary tumor, the primary tumor very likely having been in the right eye which had been removed previously. Recently Woll and Vickery (1947), and Leach (1947) each reported another instance.

The literature of primary malignant tumors was also reviewed by Whorton (1949), who collected approximately 100 cases of primary malignant tumors of the heart. He reported a primary reticulum cell sarcoma, 16 similar instances of which had been observed previously. Large masses of lymph nodes were present beneath the arch of the aorta. In the diaphragm small masses of nodes containing neoplastic tissue were present and the para-aortic lymph nodes were also involved Inasmuch as a large mediastinal tumor mass was also found it must be considered whether this may not have been the primary tumor and the masses in the atrium of the heart may not have represented metastatic lesions.

The following types of sarcomas have been reported: fibrosarcoma, leiomyosarcoma, myxosarcoma, angiosarcoma, reticulum cell sarcoma, rhabdomyosarcoma and round, spindle, and mixed cell sarcomas. Also primary lymphosarcomas are supposedly found in the myocardium. Yater stated that the majority of sarcomas of the heart arise from the atria, particularly the right atrium, from the inter-atrial septum, and from the pericardium. Mahaim also found the right atrium to be frequently involved. It may be of interest to mention that a primary sarcoma of the heart was found by Bryant (1907) in a dog.

Round and Spindle Cell Sarcoma. Perhaps the most common sarcomas are described as round and spindle cell sarcomas (Figures XII-10, XII-11 and XII-12). Mahaim found 18 round cell sarcomas in the literature, 17 spindle cell sarcomas and 11 polymorphous cell sarcomas.

Hamilton-Paterson and Castleden (1942) described a round cell sarcoma in a heart weighing 600 grams The entire right atrium was filled with large nodules, all arising from the atrial wall. The tumor was soft and white, with areas of hemorrhage, and one tumor nodule had grown through the inter-atrial septum and projected as a red mass into the left atrium. Microscopically, the cells were large and round with



Figure XII-10 Sarcoma of heart (Courtesy of Armed Forces Institute of Pathology, Acc 100,969, Neg 77204)

scanty eosinophilic cytoplasm, there were one or two areas with very large cells having giant nuclei, but no true giant cells were seen. There were no metastases. A typical spindle cell sarcoma, reported by Holer (1937), was encountered in the right atrium of a 26-year-old woman, and had produced metastases to the lungs. A primary sarcoma, situated in the left atrium was observed by Adamson (1948). It consisted of spindle, round and giant cells and had produced metastases to the duodenum, jejunum, ileum and ascending colon.

Rhabdomyosarcoma. Rhabdomyosarcomas are rarer than spindle or round cell sarcomas Mahaim mentioned only seven instances

Leach (1947) reported an additional such tumor in a 14-year-old boy The heart weighed 350 grams. A slight bulge, slightly paler than the rest of the heart, could be seen about the middle of the anterior wall of the left ventricle. A large yellowish polypoid tumor, 5.5 cm. in diameter, growing from the myocardium, filled the cavity of the left ventricle. The base of the tumor involved the anterior wall and the interventricular septum of the left ventricle and ex-

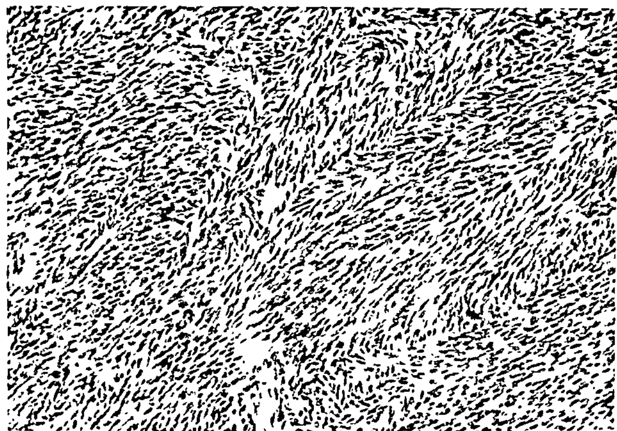


Figure XII-11 Spindle cell sarcoma Same case as Figure XII-10. X 85 (Courtesy of Armed Forces Institute of Pathology, Acc. 100,969, Neg 77250.)

tended to the anterior leaflet of the mitral valve, but did not involve it. Microscopically, the striking feature was the presence of areas of ribbonlike bands of cells, branching occasionally and showing longitudinal striations The cytoplasm was acidophilic and the nuclei were centrally located and oval, with a reticular chromatin network and very small single nucleoli There were many thin-walled blood vessels. Metastases were found in mediastinal lymph nodes, pleura and intercostal muscle.

Fibrosarcoma. Rare too are fibrosarcomas. Woll and Vickery's (1947) report concerned a 47-year-old woman. The heart weighed 310 grams and its chambers were moderately hypertrophied and dilated, especially those of the right side and the left atrium: The lumen of the mitral valve appeared to be completely occluded by a pale, yellow, firm, slightly lobulated, polypoid tumor, firmly attached by a broad base to the atrial surface of the posterior leaflet and the adjacent atrial wall. The external surface of the tumor was alternately yellow, smooth and firm, and pale pink, granular and friable. On cross-section the growth fused imperceptibly with the endocardium and formed a coarse, pale gray, homogeneous firm mass with poorly delineated radially arranged bands separating adjacent peripheral lobulations. Microscopically, the tumor consisted of relatively acellular, irregularly arranged bundles and whorls of collagenous fibers with connective tissue cells of various sizes and shapes. Most of these cells appeared to be mature fibroblasts, others had plump spindle-shaped vesicular nuclei with abundant granular cytoplasm or delicate extracellular fibrillar projections. Still others were stellate or round with large hyperchromatic nuclei. There were also a

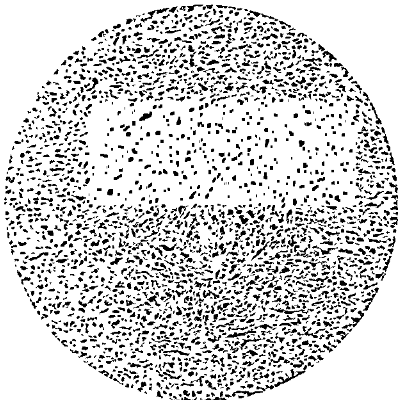


Figure XII-12 Spindle cell sarcoma of myocardium It could not be decided whether this was a rhabdomyosarcoma or fibrosarcoma Hematoxylin and eosin X 100 (WCGH, 45 P191 W)

few tumor giant cells with amorphous dark nuclei. A solitary metastatic lesion involved a thoracic vertebra In retrospect, from the description and the accompanying illustration disclosing thick bundles of fibers with palisading nuclei, it seems that this instance, as well as a number of other instances of fibrosarcoma of the heart, might fall into the classification of neurofibrosarcoma.

A primary tumor which took its origin either from the myocardium of the left ventricle or, perhaps, from the pericardium was described by Friedman and associates (1945) In the differential diagnosis, leiomyosarcoma and fibrosarcoma were considered It is interesting that a single metastasis was found in the myocardium adjacent to the aortic ring

Fibromyxosarcoma. Very rarely malignant tumors of the heart arise at the root of the pulmonary trunk. Haythorn and associates (1941) described multiple fibromyxosarcoma arising just above the pulmonary valve, within the pulmonary trunk, attached to the posterior wall about 3 cm. above the corpus arantii of the middle semilunar cusp These tumors were described grossly as myxomatous "polyps." Their pedicles were united in a common broad base. Microscopically, a striking feature of the "polyp" was the great excess of myxomatous stroma in comparison with the cellular elements. Some of the cells were spindle-shaped with long stellate processes and others were round or oval Many of the cells were multinucleated and appeared to be true neoplastic forms. Mitoses were numerous in some fields. From the microscopic description the tumor can perhaps be interpreted as a thrombus undergoing organization and also degeneration. However, a seemingly similar tumor was found in the main bronchus

on microscopic examination. The fact that these lesions were also encountered in branches of the pulmonary arteries certainly does not mitigate against the assumption that they are thrombi. The authors paid special attention to a zone of pulmonary arteritis about the pedicle of the tumor which was covered with an organizing thrombus that showed no neoplastic changes. The association of pulmonary arteritis with the base of the tumor suggested to them that the logical sequence in the development of the tumor may have been as follows: pulmonary arteritis with loss of endothelium, "protective" thrombosis, organization of the thrombus with myxomatous metaplasia, sarcomatous change in the myxoma and secondary extensions to the lungs by way of branches of the pulmonary arteries. The authors thus explain the tumor as occurring on the basis of changes within a thrombus.

Polymorphous Cell Sarcoma. A polymorphous cell sarcoma involving the pulmonary artery was described by Martin and associates (1939). It was polypoid, measured 2 5 cm. in diameter, involved the pulmonary valves and the adjacent endocardium, and extended also along the course of the pulmonary trunk to the right and left pulmonary arteries. There were no metastases.

Sites of Metastases. Metastases of primary sarcoma of the heart may be widespread. In Yater's (1931) series of 46 cases, metastases were found in 21. The organs and frequency of their involvement were: lungs, 8 times, lymph nodes, 5 times; pancreas, 4; suprarenals, 3; and liver and kidneys, each twice. In Mahaim's series of 87 cases, the organs and frequency of involvement were: lungs, 24; lymph nodes, 9; liver, 9; kidneys, 8; suprarenals, 7; pancreas, 5; and intestines, 3 times.



Figure XII-13. Tumor of intra-atrial portion of septum diagnosed lymphangioendothelioma. This tumor should be classified as a mesothelioma arising from the node of Tawara. X 7. (From Perry, C B, and Rogers, H. Lymphangioendothelioma of the heart causing complete heart block, *J. Path and Bact*, 39 281-284, 1934 Reproduced by courtesy of the publishers)

Mesothelioma of the Myocardium

There is a group of tumors of disputed origin which occur in the region of the atrioventricular node. Today, most of these tumors (Figure XII-13) are classified as mesotheliomas (coelotheliomas, originating from misplaced epicardial structures). Apparently the first case of this type was described in 1911 by Armstrong and Monckeberg. These authors described a tumor in a 5½-year-old boy who had had complete heart block. It was not recognized grossly but only on histologic examination. The tumor was characterized by the presence of spaces which were lined by one or two rows of endothelial cells surrounded by dense connective tissue; a number of cords consisting of cells similar to those lining the spaces were also noted (Figure XII-14). The atrioventricular node was located adjacent to the tumor. This new growth was interpreted as a *lymphangioendothelioma*.

Lloyd in 1929 described an apparently similar tumor in a 39-year-old woman who clinically had had partial heart block with



Figure XII-14 Tumor of region of node of Tawara, classified as mesothelioma Note small pseudoglandular structures lined by cells interpreted as mesothelial cells (From Mahaim, I *Les Tumeurs et les Polypes du Coeur* Masson et Cie, Paris, 1945 Reproduced by courtesy of the publishers)

prolonged conduction time The clinical diagnosis was syphilis of the myocardium but no syphilitic lesions were encountered in either the aorta or heart. There were no gross alterations in the contour of the interventricular septum but on cross-section of the septum vaguely outlined clusters of minute cystic spaces, surrounded by a whitish translucent fibrous stroma, were observed, some of which contained a clear yellowish coagulum. On microscopic examination a definitely neoplastic structure was recognized in the form of cystic spaces lined by several irregular layers of cells, most of which were round or slightly elongated with indefinite cell boundaries. Some of the spaces were separated from each other by a dense fairly cellular connective tissue In some areas clumps of round or oval tumor cells with vesicular nuclei were arranged in solid cords which, on examination of numerous serial sections, failed to reveal any true tubular structures. A number of the cystic spaces had invaded the region of the atrioventricular node, which contained a few scattered bundles of muscle fibers that were smaller than those of the remainder of the myocardium. Lloyd (1929), and Armstrong and Monckeberg believed that since the atrioventricular node is especially rich in lymphatics and since the tumors, according to their interpretation, consisted of lymph vessels and proliferation of endothelial cells lining these vessels, they should be classified as lymphangioendotheliomas. The localization of the tumor reported by Lloyd readily explains the clinical finding of heart block and, perhaps, the sudden death of his patient.

Grant and Camp (1933) reported a vascular tumor located in the region of the atrioventricular node. This tumor had produced complete heart block and was recognized only on microscopic examination. It was found in the region where the atrioventricular bundle normally bifurcates, and extended through the entire width of the septum, bulging outward at the base of the tricuspid valve to form a small nodule. It consisted of a compact leash of tortuous, irregularly dilated and anastomosing blood vessels, chiefly arterial in structure, and was not sharply limited at its margin. They believed that this tumor should be classified as a rare arterial angioma However, no detailed description of the vessel walls and their lining cells are given and it would seem likely that this tumor falls into the same classification as those described by Armstrong and Monckeberg, and by Lloyd

Another apparently similar tumor which had also caused complete heart block was described by Perry and Rogers in 1934. On gross examination the heart was normal in size and a minute tumor was found just between the interventricular and interatrial septa, bulging slightly into the left ventricle. Microscopically the tumor closely resembled those described by Armstrong and Monckeberg, and by Lloyd and was also interpreted as a lymphangioendothelioma. By serial sections the gradual

approach of the tumor to the atrioventricular bundle, its entry at the superior angle of the bundle, and the final complete involvement of the conduction tissue were easily observed.

A detailed description of another similar tumor classified, however, as a primary epithelial tumor, was given by Rezek (1938). This tumor was found in a 71-year-old patient in whom, electrocardiographically, a transitory complete heart block was diagnosed. At postmortem examination a diffusely infiltrating carcinoma of the stomach was found with metastases to the regional lymph nodes. Only on microscopic examination was a tumor found very close to the atrioventricular node. It consisted of a number of channels, lined by one or two layers of cuboidal cells, resembling and interpreted as epithelial cells. The specific muscle fibers in the region of the tumor were atrophic and occasionally disclosed actual necrosis. A moderate amount of scar tissue and foci of calcification, minute areas of hemorrhages, and infiltration of lymphocytes were found close to the tumor. Because of the morphologic appearance of the tumor, malignancy was ruled out. It was especially emphasized that this tumor could not possibly be interpreted as a metastasis from the primary carcinoma of the stomach. Rezek pointed out a close resemblance between the cystic structures of this tumor and their lining cells, and the glandular structures found in the embryonal intestinal tract. He recalled that in serial sections of very young embryos a close local relationship is noted between the cardiac Anlage and the anterior wall of the primitive foregut. He concluded that it is possible that those cystic structures of which the tumor consists may arise from heterotopic epithelium of the foregut, displaced in the heart during an early stage of embryonic development. For this reason, Rezek classified this tumor as epithelial. Because of the histologic similarity of this tumor and these described by Armstrong and Monckeberg, Lloyd, and Perry and Rogers, Rezek concluded that all these tumors are obviously of the same origin. Leicher (1948) concluded that the glandlike structures in his tumor were epithelial in nature. He thought that they were hamartomas arising from misplaced caudal portions of the primitive gut.

Still a different origin for these tumors, which seems to be the most likely one, was advanced by Mahaim (1945). He reported a tumor in the heart of a 24-year-old woman who had had a complete heart block clinically. The tumor was located in the region of the node of Tawara and corresponded in every detail to those just described. Mahaim stated that this is a primary benign multilocular tumor. The tumor always produces complete or partial heart block by destruction of the atrioventricular node in its posterior portion. However, he emphasized that this tumor is neither a lymphangioendothelioma nor an epithelial tumor, but originates from proliferated embryonal epicardial (mesothelial) cells during the early stage of the development of the node. Thus, it should be classified as a *mesothelioma* (coelothéliome Tawarien bénin).

In this connection must be mentioned a rather unique lesion of the heart, which was reported by Dosch (1941). He described a nodular tumor interpreted as an accessory thyroid nodule, within the interventricular septum, bulging beneath the endocardium into the right ventricle just below the pulmonary valve. He does not believe that this structure represents misplaced thyroid tissue but should be interpreted as the end-result of growing dedifferentiated entodermal epithelium. Dosch mentioned that such dystopic thyroid tissues have been described several times in the heart of the dog. He discussed

the possibility that certain lymphangioendotheliomas and mesotheliomas, arising in the interventricular septum, may perhaps also be examples of such accessory thyroid nodules. However, it is well known that occasionally benign-appearing nodular colloid goiters which in all likelihood *harbor a minute malignant tumor* produce metastases (so-called metastasizing colloid goiter). Dosch does not mention examination of the thyroid in his case and thus the question must be raised whether or not the thyroid structure found in the septum of the heart constitutes a metastatic nodule of a primary so-called *metastasizing colloid goiter.*

A tumor of the right atrium consisting of both myxomatous and glandlike or cystic structures of the type just discussed was described by Anderson and Dmytryk (1946). Microscopically, most of the tissue had a myxomatous appearance and was composed of relatively few cells *within an abundant, loose, pale-staining* stroma which was faintly basophilic or eosinophilic. Glandular cystlike spaces lined by cells resembling epithelium were noted in various areas of the tumor. The lining cells varied from flat cells of endothelial type to tall, closely packed, columnar cells with basal nuclei. The authors *advanced three possible explanations of* the cystlike spaces: (1) They represented lymph vessels, (2) they were derived from heterotopic inclusions of entodermal tissue of the primitive foregut, or (3) they were of pericardial (mesothelial) origin. Anderson and Dmytryk were inclined to believe that the evidence favored a pericardial origin of the epithelium-like structures, and that mesothelial cells of the visceral pericardium have often been observed to differentiate into tall columnar cells, as encountered in their tumor.

A tumor involving the inferior vena cava, right atrium, right ventricle and the epicardial surfaces of the aorta and pulmonary trunk, was reported by Reisinger and associates (1942). From the description it is difficult to venture an opinion whether (1) *this tumor was primarily located* in the wall of the vena cava, (2) the primary tumor was located in the heart, or (3) there were primary lesions in both vena cava and heart. Histologically, irregularly elongated cells were found with large, round or oval nuclei and a scanty cytoplasma which stained faintly eosinophilic. *Intermingled with these cells were roughly* polygonal or round cells with eccentrically placed bean-shaped nuclei which occupied more than half of the cells. The cytoplasm took a faint neutral stain and contained no granules. There were scattered lymphocytes and polymorphonuclear leukocytes and an occasional eosinophilic leukocyte. *The belief is expressed that this* tumor should be classed among "endotheliomas."

METASTATIC TUMORS OF THE PERICARDIUM AND HEART

Metastatic tumors of the heart are much *commoner than primary tumors (Figure* IX-15). The literature does not give a correct account of the actual frequency of occurrence of metastasis to the heart, since usually only those instances are reported in which the metastases were evident grossly. In my experience, foci of metastatic tumor cells are occasionally encountered in the myocardium, if enough blocks are cut *and examined histologically even though* grossly no tumor is present. Reiling and Razinsky (1941) also stated that from recent studies of large series of autopsies it is apparent that metastatic tumors of the heart occur more commonly than is ordinarily believed. McCandless and Faloon (1948) diagnosed metastatic carcinoma of

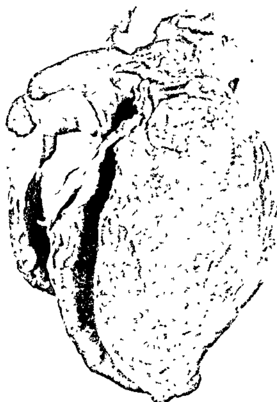


Figure XII-15 Metastatic carcinoma of pericardium The primary tumor was a squamous cell carcinoma of the esophagus

the pericardium by cytologic examination of the pericardial exudate.

Incidence. In the literature many reports of series of metastatic cancer are labeled merely metastases to "the heart and pericardium" and often no distinction is made as to whether the heart, the pericardium or both are involved.

Bryant (1907) found nine instances of metastases to the heart among 2492 autopsies at Johns Hopkins Hospital; Karrenstein (1908) reported 15 secondary carcinomas, eight of which were to the pericardium and four secondary sarcomas of the pericardium among 6655 autopsies. Bardenheuer (1924), among 1275 instances of malignant tumor, reported 30 secondary tumors (2.3 per cent) in the heart, the myocardium being involved only eight times. Benjamin (1939) found an incidence of 0 5 per cent secondary carcinoma among 40,000 autopsies. Pollia and Gogol (1936) recorded 220 secondary tumors in the heart among 46,072 autopsies (0.48 per cent) as collected from the literature. Lymburner (1934) found 52 among 8550 autopsies. Scott and Garvin (1939) stated that among 1082 instances of malignant disease appearing in a series of 11,100 autopsies, the heart was involved by metastases in 79, the parietal pericardium in 61, the heart and parietal pericardium together in 22, and the heart or parietal pericardium, or both, in 118. Ritchie (1941), in an autopsy material of slightly over 3000, reported 16 metastatic tumors (0 53 per cent) in the heart and, in addition, 23 with metastasis to the pericardium. Lisa and associates (1941) collected from the literature reports of 119 tumors of the heart; of these 72 were primary in the heart and 47 were metastatic Prichard (1951) found, among 4375 autopsies on patients with various cancers, 146 (3.4 per cent) with metastasis to the myocardium. Willis (1948) stated that fragments of growth carried in the systemic venous blood rarely become attached to the chordae or cusps of the tricuspid valve or to other parts of the endocardial surfaces of the right chambers of the heart, and grow into branching or nodular masses. He also remarked that this occurs most frequently with teratomas of the testis, but also with alimentary and other carcinomas. Left-sided endocardial implants from tumor fragments carried in the pulmonary veins are still rarer.

Primary Site. Yater (1931) stated that metastasis to the heart has occurred from malignant neoplasms of all the main organs. Table XII-6, taken from Scott and Garvin (1939), is included to show the type and location of the primary tumor and the localization of the cardiac metastases.

Types of Malignant Neoplasm. In many reports it is difficult to decide whether the involvement of the pericardium by bron-

TABLE XII-6

Source of 118 Secondary Tumors of the Pericardium and Heart (Scott and Garvin, 1939)

Primary Tumor	*Number of Cases*	*Metastasis to Heart*	*Metastasis to Parietal Pericardium*	*Metastasis to Both Heart and Parietal Pericardium*	*Metastasis to Heart or Parietal Pericardium or Both*
Carcinoma of bronchus	115	30	26	15	41
Carcinoma of breast	45	3	13	0	16
Reticulum cell sarcoma	9	6	0	0	6
Melanoma	10	5	2	2	5
Lymphatic leukemia	11	6	0	0	6
Chloroma	3	2	0	0	2
Leiomyosarcoma	6	1	2	0	2
Carcinoma of bladder	25	0	1	0	1
Carcinoma of cervix	49	2	0	0	2
Carcinoma of colon	27	0	1	0	1
Carcinoma of esophagus	61	2	2	0	4
Carcinoma of kidney	19	3	1	1	3
Hypernephroma	12	1	0	0	1
Carcinoma of liver	21	2	1	0	3
Carcinoma of pharynx	9	1	0	0	1
Carcinoma of lip	5	1	0	0	1
Carcinoma of ovary	19	1	0	0	1
Carcinoma of pancreas	45	2	2	0	4
Carcinoma of prostate	56	0	2	0	2
Carcinoma of rectum	39	2	2	1	4
Carcinoma of stomach	201	1	1	0	2
Metastatic carcinoma (primary undetermined)	16	2	1	1	2
Neurofibrosarcoma	2	1	0	0	1
Retroperitoneal sarcoma	2	0	1	0	1
Liposarcoma	1	1	0	0	1
Round cell sarcoma	4	1	0	0	1
Lymphosarcoma	13	1	1	1	1
Hodgkin's disease	22	0	1	0	1
Myelogenous leukemia	14	2	1	1	2
Miscellaneous *	221	0	0	0	0
	1,082	79	61	22	118

* Refers to a variety of tumors which in this series did not metastasize to the heart or pericardium.

chogenic carcinoma represents true metastasis or direct extension from the primary tumor to the pericardium Whenever this distinction has been made, it will be indicated

Among 52 metastatic tumors in Lymburner's (1934) series, there were 36 carcinomas and 16 sarcomas, of which six were malignant melanomas. From Table XII-6 it is clear that any malignant tumor may occasionally produce metastasis to the heart Of all primary carcinomas, apparently carcinoma of the bronchus is the most frequent source of secondary tumors of the pericardium and heart (Reuling and Razinsky, 1941) Among 66 instances of carcinoma of the lung in Herbut and Maisel's (1942) series, the heart was involved eight times. Kaufmann (1922) stated that malignant melanotic tumors metastasize frequently to the myocardium. In my own experience, malignant melanoma is the malignant tumor which most frequently produces metastasis in the myocardium.

Among 81 metastatic tumors of the heart Raven (1948) found only three malignant melanomas. In his series the most common primary tumor was located in the breast.

A metastatic carcinoma of the pericardium which had produced a syndrome of constrictive pericarditis was reported by Wallace and Logue (1946) The primary tumor was a bronchogenic carcinoma.



Figure XII-16 Metastatic neoplasm of right ventricle from primary adenocarcinoma of stomach.

A seemingly unique case, in which a primary myoblastoma of the region of the left groin had produced metastases to the heart, was described by Khanolkar (1947). Grossly the myocardium was sprinkled with tumor nodules, many of them being

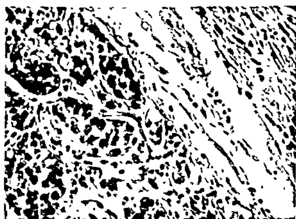


Figure XII-17 Carcinoma metastatic to myocardium. The primary tumor was a carcinoma simplex of the breast Hematoxylin and eosin X 350

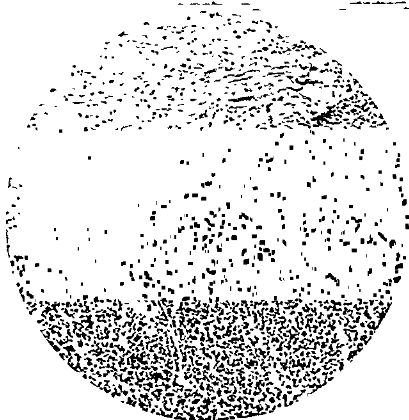


Figure XII-18. Malignant melanoma metastatic to myocardium. Hematoxylin and eosin X 100. (WCGH, 45 P 191 X.)

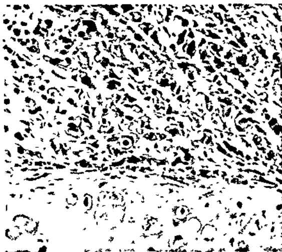


Figure XII-19 Primary squamous cell carcinoma of bronchus which gave rise to implanted lesion on tricuspid valve (see Figures XII-20 and 21) X 400 (WCGH, 50 P 628) (Courtesy of Dr F C Coller)

beneath the endocardium These nodules seemed more numerous on the papillary muscles, giving the latter a peculiar beaded appearance A testicular teratoma with extensive intracardiac metastases was reported by Watts (1947) Rabson's (1938) mesenchymal hemendothelioma produced metastases to the right atrium.

There are rare instances of a primary malignant tumor breaking through a large vein and actually migrating into the right atrium and ventricle. This occurrence has been reported in primary malignant tumors of the kidney by Oberndorfer (1907). (See also Kaufmann, 1922, for further references.)

Tumor implantation upon the mural endocardium or valvular endocardium is very rare. However, there are a few cases on record which show that tumor cells may become implanted on the heart valves. A pertinent case was reported by Coller and associates (1950). The primary tumor was a bronchogenic carcinoma (Figure XII-19). Several clusters of soft delicate vegetations were attached to the chordae tendineae and the papillary muscles of the right ventricle and to the posterior cusp of the tricuspid valve (Figure XII-20). The vegetative growth was grayish white and cauliflower-like. The mitral valve also contained two similar vegetative growths. Microscopically, nests of tumor cells were found in small groups or scattered throughout the dense fibrinous and granular material (Figure XII-21). It is interesting to speculate on whether these hearts have had primarily an acute vege-



Figure XII-20 Vegetation on tricuspid valve containing metastatic carcinoma, from primary bronchogenic carcinoma (cf. Figure XII-19). (From Coller, F. C, Inkley, J J, and Moragues, V Neoplastic endocardial implants, *Am J Clin. Path*, 20 159, 1950 Courtesy of authors and The Williams and Wilkins Co.)

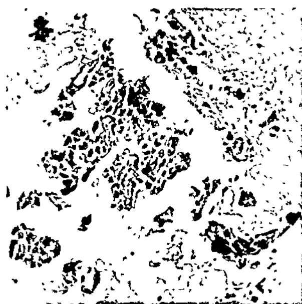


Figure XII-21. Photomicrograph of vegetation shown in Figure XII-20 X 400 (WCGH, 50 P 628) (Courtesy of Dr F C. Coller.)

tative (bacterial) endocarditis with secondary implantation of tumor cells. Coller and associates thought it probable that a certain amount of valvular damage is a prerequisite for tumor implantation. Rockenschaub (1950) reported carcinomatous implants on the endocardium of the right ventricle in a subject with squamous cell carcinoma of the cervix.

Mode of Spread to Heart. The various modes of involvement of the pericardium and heart are discussed by Scott and Garvin (1939) and are indicated in Table XII-7.

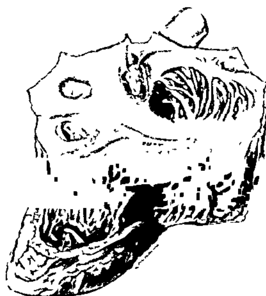
TABLE XII-7

Frequency of Various Modes of Involvement of the Pericardium and Heart by Secondary Tumors, According to Scott and Garvin (1939)

	Site of Metastasis	
Mode of Involvement	*Parietal Pericardium*	*Heart*
Definitely hematogenous	8	37
Definitely by extension	25	18
Definitely lymphatic	3	0
Probably hematogenous	6	5
Probably by extension	2	1
Probably lymphatic	7	0
Combination of routes	2	4
Undetermined	8	14
	61	79

Portion of Heart Involved. Yater (1931) and Kirch (1927) and also Mahaim (1945) stated that the right side of the heart is more often involved than the left side. In Scott and Garvin's series, however, more secondary tumors occurred in the left side of the heart than in the right. In their cases the parietal pericardium was involved 61 times, the right atrium, 29; right ventricle, 31; left atrium, 29; left ventricle, 45; and interventricular septum, 11 times In six cases neoplasm was found only upon microscopic examination. The endocardium alone may be involved. Herbut and Maisel (1942) mentioned four instances in which the mural endocardium, and four other instances in which the valvular endocardium was involved. Mahaim classified cardiac metastases into those involving the mural and valvular endocardium, septal tissue, and other areas which were "silent."

A metastatic carcinoma to the interventricular septum, diagnosed clinically because of a pulse rate of 26 to 28 per minute was reported by Rosler (1924). The pri-



Figu... of ri... cava, ... carcinoma of cervix. (Drawing by Louise Home, Wayne County General Hospital.)

mary carcinoma arose from the skin of the cheek.

"Marantic Endocarditis" (Nonbacterial **Thrombotic Endocarditis).** Certain changes, other than metastasis, are described in the endocardium and myocardium in patients who die of cancer; in the valvular endocardium these changes are similar to so-called marantic endocarditis. According to Eger (1941), Guder found 169 instances of recent verrucous endocarditis among 12,705 autopsies. Among these 169 autopsies there were 43 instances of cancer, in 40 of which the subjects revealed no evidences of an acute infectious disease. Such an endocarditis occurring in cancer patients in the absence of an acute infectious process, is sometimes referred to as "cancer endocarditis" (Eger). The endocardial changes are explained as follows. shortly before the death of the patient there is absorption of toxic substances which causes an activation of the mesenchyma and also damages the endothelial lining of the heart valves. In the region of these defects the blood plasma extends into the valvular tissues and causes a fibrinoid degeneration with consequent formation of thrombi. Eger concluded that split products of the carcinoma are toxic and cause the allergic reaction. (See also Allen and Sirota, 1944.)

Eger also described interstitial myocardial granulomas consisting principally of histiocytic cells in patients who died of cancer. Among 34 hearts with endocarditis, from patients with carcinoma, such changes were found eight times. In not a single instance were typical Aschoff bodies recognized

CYSTS OF THE MYOCARDIUM AND HEART VALVES, AND DIVERTICULA

Epithelial Cysts

Simple epithelial cysts (Figure XII-23) also occur within the heart but are very rare. Davidsohn in 1938 was able to find only three instances in the literature, to which he added a fourth. These cysts were *encountered as incidental findings.* Stoekenius (1919) reported a pea-sized cyst in the posterior papillary muscle of the left ventricle. The inner surface of the cyst was lined by ciliated epithelial cells, varying from columnar to cuboidal to flat cells, the latter resembling the lining endocardial cells. In some cells the nuclei were pushed to the periphery, producing a resemblance to goblet cells. He attempted to explain these cysts on the basis of persistent unused minute cavities, dating back to the embryonal period when the cavity of the heart had the structure of a sponge. Kolatschow (1933), who reported a cyst (21 × 18 × 17 mm.) close to the anterior papillary muscle of the left ventricle, suggested either heterotopic glandular structures or misplaced epicardial lining cells as the possible origin of this cyst. (See also Leicher, 1948)

De Chàtel (1933) found two cysts in the interatrial septum of a newborn girl. *They were lined by squamous cells.*

Davidsohn found a cyst measuring 10 × 5 × 4 mm. on the posterior wall of the left ventricle within the posterior papillary muscle near its tip. It was an incidental finding in a 64-year-old woman, who died of general peritonitis following operation for perforation in adenocarcinoma of the cecum. Microscopic examination of the *cyst disclosed its inner surface to be lined* by two layers of epithelial cells, covered by cilia. Mayer's mucicarmin stain showed *areas staining deep red at the periphery of* the cystic cavity, adjacent to the lining cells. Davidsohn called attention to the similarity in structure between such a very



Figure XII-23 Congenital cyst of myocardium X 150. (WCGH, 45 P 191 A.) (Courtesy of Dr. B E Stofer)

rare epithelial cyst of the heart and the not uncommon esophageal cyst which is lined with a columnar, frequently ciliated, epithelium or with squamous cells. The lumen of these cysts is always completely separated from the lumen of the esophagus. It is accepted that the esophageal cyst is caused by a disturbance in the separation of the trachea from the intestinal tract. Davidsohn pointed out that whereas such an explanation for the esophageal cysts is convincing there is no bridge that would permit the application of this hypothesis to the epithelial cysts of the heart.

Leighton and associates (1950) also found squamous epithelial cysts in the heart of an infant at the root of the septal leaf of the tricuspid valve and the adjacent septum, along with a saccular deformity. The interventricular septum was patent. The cysts were multilocular and were lined by non-keratinizing stratified squamous epithelium. Some of the cystic spaces contained an amorphous debris and shrunken cells with clear cytoplasm and pyknotic nuclei. There were also cystic changes in the ovaries and breasts.

Sachs and Angrist (1945) reported a small cyst situated in the center of the left ventricular wall, measuring 0.9 cm. in diameter. It was completely surrounded by cardiac muscle and did not cause any discernible bulging of the muscle toward either the epicardial or the endocardial surface. The contents of the cysts were gelatinous and translucent, with a pale greenish tint. On microscopic examination the inner layer was formed by epithelium which was tall columnar for the most part and ciliated, but more cuboidal in other areas.

The authors suggested that such cysts arise through the heterotopic inclusion and sequestration of entoderm during the formation of the primitive foregut and single-chambered heart. Bayer (1940) described

a cyst arising just beneath the epicardium close to the apex of the heart. The cyst was lined by endothelial cells and was interpreted as originating from misplaced epicardial cells. He also described a cyst in the myocardium lined by ciliated epithelial cells in a patient who had died of carcinoma of the large intestine. This cyst was interpreted as arising from misplaced epithelium of the bronchial tree.

Summary. If microscopically a number of small glandlike structures are encountered in the heart, especially in the region of the atrioventricular node, it is most likely that they represent misplaced pericardial lining cells. If they form tumors, they must then be interpreted as mesotheliomas. If cysts are present which are lined by cells of questionable origin, they may also be regarded as arising from mesothelial cells. If they are ciliated they may be considered to arise from misplaced epithelium of the bronchial tree. If the cells are squamous in type, they arise either from misplaced ectodermal or from entodermal cells which have undergone metaplasia. From a review of the reported instances of cysts in the myocardium, one is struck by the fact that in many of these patients, in addition to the cysts, a primary carcinoma was also present, commonly located in the gastrointestinal tract. In the cases cited, the authors discussed, but always ruled out, the possibility that the cysts represented metastatic lesions. (See also Mesotheliomas of the Heart.)

Blood Cysts (Telangiectases)

Blood cysts (telangiectases) are often found on the heart valves of newborn infants. According to Levinson and Learner (1932), they were recorded as early as 1844 by Elsaesser and 1857 by Luschka. They are described as small, circumscribed, elevated, dark red nodules which appear grossly as cysts filled with blood. They are seen most commonly on both the mitral and tricuspid leaflets, usually vary from pinpoint to pinhead size and rarely exceed 1 mm. in diameter. They vary in number from two or three to 10 or 15 but as many as 30 have been reported in one heart. The nodules project above the atrial surface of the atrioventricular leaflets near the free margin between the edge and the line of contact or closure. On the semilunar cusps the nodules project into the ventricle and are located at or very close to the line of attachment of the cusps.

The rare occurrence of a hemangioma (blood cyst?) was reported by Prichard (1951) in the right atrium in the region of the foramen ovale in a 38-year-old white man.

Valves Involved. Table XII-8, taken from Jonsson's (1916) communication, discloses the relative frequency of the involvement of the valves.

TABLE XII-8

Distribution of Blood Cysts (Telangiectases) on Heart Valves in Jonsson's (1916) Series of Newborn Infants

Valves Involved	*Valves Showing Nodules (Cysts)*	*Number of Cases*
Mitral, tricuspid, pulmonic and aortic	4	2
Mitral, tricuspid and pulmonic	3	2
Mitral and tricuspid	2	23
Tricuspid and pulmonic	2	1
Tricuspid and aortic	2	1
Mitral and aortic	2	1
Mitral	1	7
Tricuspid	1	6
Aortic	1	1
Pulmonic	1	1
Total		45

Microscopic Appearance. On histologic examination the nodules appear on cross-section as spaces filled with red blood corpuscles. These spaces are lined by a single layer of endothelial cells, in appearance similar to the surface of the endothelium of the valve leaflet. Near the attachment of the valve to the myocardium a few blood vessels are inconstantly seen, al-

though in the body of the leaflet no blood vessels are found.

Origin. Several views have been expressed regarding the origin of these cysts (telangiectases). Some authors believe that they represent extravasations of blood and should be classified as hematomas. Others believe that they represent either true angiomas or, perhaps better, hamartomas, while still others think that these cysts represent dilated blood vessels. Another opinion holds the cysts to be spaces filled with blood, the result of blood pressed into crevices running from the surface of the leaflet into the stroma forming the leaflet. According to Jonsson (1916), the cysts develop when passing blood accumulates within these spaces or potential spaces Development of cysts depends on the specific structure of the leaflet as well as upon the character of the tissue of the leaflet Levinson and Learner (1932) concluded that there is no pathologic significance to these cystic nodules. They are to be considered as a common anatomic finding. Boyd (1949) believed that blood cysts are commonly present on the heart valves of infants. From a study by means of serial sections he supported the explanation that they result from blood being pressed into crevices on the ventricular surfaces of the cusps. Subsequent fusion of the mouths of the crevices forms the blood cyst.

Diverticula of Heart

True Diverticulum. True diverticula of the heart were recorded by Arnold (1894) and also by Mahrburg (1930). They described fingerlike outpouchings of portions of the left ventricle, which were well separated from the surrounding structures outside the heart, or which were either separated from the heart, or had extended through the opening of the diaphragm to the anterior abdominal wall. The wall of these outpouchings consisted of cardiac muscle and were lined by endocardium. Therefore, they were classified as true diverticula.

False Diverticulum. A false diverticulum was recorded by Bayer (1940). It was located at the apex and had caused adhesions between both leaves of the pericardium. It was thought that the original lesion was misplaced endocardium, which because of necrosis of proliferated endothelial cells, formed a cystlike structure, still communicating with the left ventricle. The cystic structure gradually became larger and extended into the pericardial sac. The result was an outpouching of the endocardial structures into the pericardium. It is difficult to decide whether this false diverticulum may be interpreted as an aneurysm of the heart.

LEUKEMIA AND ALLIED DISEASES

In the discussion of leukemic involvement of the heart, an attempt is made to distinguish between simple microscopic leukemic infiltration and leukemic infiltration which has assumed the proportions of a tumor. Yet, from the literature, it is sometimes difficult to decide to which classification the relevant report belongs. It is also often difficult to decide whether a given tumor should be classed among leukosarcoma (sarcoleukosis, see Hirschfeld, 1925), lymphosarcoma, chloroma or chlorosarcoma, or myelosarcomatosis. These are, of course, the same difficulties which confront one in investigating any phase of these interesting lesions. Whatever classification is adopted, whatever the true nature of these lesions may be, it must



Figure XII-24. Fibrinosanguineous pericarditis resulting from infiltration by monocytic leukemia. (WCGH 49 P 491)

be emphasized that the pericardium (Figure XII-24) and myocardium are often involved in these conditions.

Leukemia

According to Kirch (1927), leukemic infiltrations of the myocardium are found only occasionally. They occur in both lymphatic and myeloid leukemias. These infiltrations may be confined to the stroma and may be confused with myocarditis. I have observed leukemic patients, with severe leukemic infiltration of the myocardium, who died unexpectedly. Often the pericardium is also involved. In fact, Wendkos (1941) described an instance in which massive pericardial effusion, because of leukemic involvement of the pericardium, was the earliest and outstanding manifestation

More recent references indicate that leukemic infiltration in the myocardium (Figures XII-25 and XII-26) are much more commonly present than was previously assumed. This can be easily explained by more careful histologic examinations of the myocardium. Thus, Aronson and Leroy (1947) concluded that the heart is frequently involved in leukemia. Furthermore, Wintrobe and Mitchell (1940) reported the occurrence in patients with leukemia of initial symptoms suggesting cardiac disease. One of their patients came to autopsy and disclosed a myeloid chloroma with cardiac involvement.

Kirshbaum and Preuss (1943) studied 123 fatal cases of leukemia and found the heart involved in 43 (34 per cent). The leukemic cells were encountered within the capillaries and in the interstitial tissue between the myocardial fibers Among 11 patients with acute lymphatic leukemia the heart was involved in six (54 per cent). The highest percentage of cardiac involvement was found in acute stem cell leukemia Of 23 such instances, leukemic infiltrations in the myocardium were encountered 14 times (61 per cent). As stated above, Wendkos (1941) reported massive involvement of the pericardium and myocardium in a patient with acute lymphatic leukemia who died unexpectedly

Among 95 instances of various forms of



Figure XII-25 Myocardial involvement in lymphoblastic leukemia Note blood vessel filled with immature leukocytes Iron-hematoxylin X 125

leukemia which were studied at Michael Reese Hospital and carefully examined microscopically for the presence or absence of myocardial involvement, leukemic infiltrations were found in 34 hearts (36 per cent). The above figures, therefore, indicate that the myocardium is commonly involved in leukemia.

Reim (1916) reported an instance of acute lymphatic leukemia with tumorous nodules in the endocardium, in which the question arises whether the classification should not rather be lymphosarcomatosis or, perhaps, *sarcoleukosis* Low (1910) reported such an instance of myeloid cell



Figure XII-26. Leukemic (lymphoblastic) infiltration of myocardium. Hematoxylin and eosin X 100

infiltration at the base of the interventricular septum.

While leukemic infiltrations are thus commonly encountered, Forkner (1938) has stated that the progressive heart failure sometimes observed in patients with leukemia is caused in all probability by myocardial degeneration, anemia and *anoxemia.*

Three apparently unique cases may be quoted here Costa (1931) attributed rupture of the left atrium of the heart to leukemic infiltration (myeloid leukemia). Puech and associates (1932) reported unexpected death in a patient with acute leukemia. At autopsy, a leukemic thrombus was found completely filling the ventricles of the heart Koberle (1937) described leukemic infiltrations in the heart valves.

Chloroma and Lymphosarcoma

Chloromas also involve the heart. A typical instance of myeloid chloroma was described by Mieremet (1914). Green nodules were found in the anterior wall of the left ventricle and posterior wall of the *right ventricle. Lymphosarcoma* involves the pericardium much more often than the myocardium. Among 23 cases of metastases to the pericardium in Mieremet's series, there were five lymphosarcomas. Among his 16 instances of metastases to the myocardium there was only one lymphosarcoma, but the gross data were incomplete. Interesting is the report of Bardenheuer (1924) who found a primary lymphosarcoma of the ileum, which had metastasized to the right atrium and right ventricle and had produced severe stenosis of the tricuspid orifice.

As far as leukosarcomas are concerned, Forkner (1938) states that leukosarcoma, when situated as it is so often, within the *anterior mediastinum,* frequently invades the pericardium and also the myocardium.

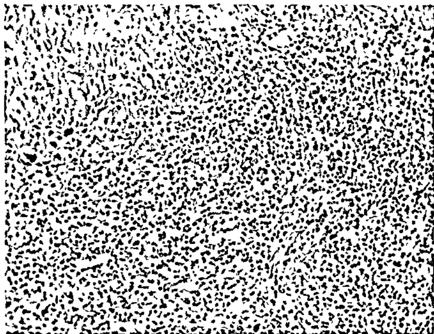


Figure XII-27 Hodgkin's nodules of myocardium Note area of fibrosis and a few multinucleated Dorothy Reed cells Hematoxylin and eosin X 100 (WCGH, 45 P 191 Y)

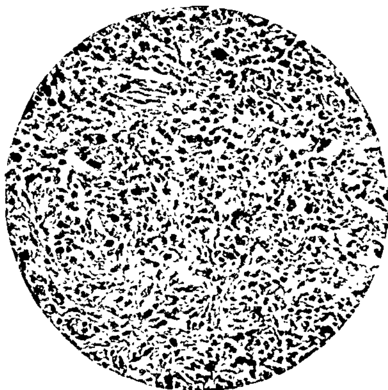


Figure XII-28 Hodgkin's disease infiltrating heart Hematoxylin and eosin X 800 (WCGH, 435-38)

Myeloma

Myelomas also may produce metastatic nodules in the myocardium (Lichtenstein and Jaffe, 1947). Carlisle (1938) found two nodules, each the size of a bean, in the wall of the right atrium in a patient with myeloma. Piney and Riach (1931) found in one instance of multiple myeloma a number of whitish nodules at the apex of the heart, which proved to be extramedullary metastases.

Hodgkin's Disease

Hodgkin's disease also involves the heart (Figures XII-27 and 28). In a recently observed instance of Hodgkin's disease multiple sections were cut from the myocardium and a typical granuloma was found in one. Extension of mediastinal masses into the pericardium and myocardium is occasionally seen in routine postmortem material, though many such occurrences are not reported.

Schlagenhaufer (1919) reported three cases of Hodgkin's disease of the gastrointestinal tract. In one, the heart was of a yellowish color and presented an irregular speckled appearance. Histologically, the myocardium showed typical granulomatous tissue with Sternberg-Reed cells Šikl (1933) mentioned a case in a general review on myocarditis. Dalous, Fabre and Pons (1936) reported, in a 25-year-old man with Hodgkin's disease of the mediastinum, that the myocardium showed a number of whitish spots which histologically consisted of the specific type of granulation tissue. It is interesting to note that muscle giant cells were also present which were definitely distinguished from the Sternberg-Reed type of giant cell. The patient had died suddenly. Without giving any reference, these authors quoted a case of Hodgkin's granuloma in the heart, reported by Barre and Desnos. Krueger and Meyer (1936) reviewed 60 cases of Hodgkin's disease, including 16 autopsies. The ventricular myocardium was involved twice and the right atrium once. McAlpin (1937) in a review of 23 autopsies found nodules in the myocardium recorded in two instances. Harrell (1939) reported an instance of fulminating Hodgkin's disease in which the pericardium and myocardium were involved, and Ritvo (1940) also reported an instance with involvement of the pericardium and myocardium. The pericardium and the right atrium were involved in the case reported by Garvin (1941). The Hodgkin's granulomas projected into the atrial cavity as a polypoid mass.

Setzu (1942) stated that he was able to collect only 10 instances of involvement of the heart in Hodgkin's disease He described an additional case in which both the pericardium and myocardium disclosed the characteristics of Hodgkin's granulomas. Most of the changes in this instance were encountered in the pericardium where the nodules were well circumscribed and only a few had fused.

The occurrence of numerous polypoid growths microscopically characteristic of Hodgkin's disease covering the endocardium of the left ventricle, especially between the columnae carneae, was reported by Catsaras and Patsouri (1941). These authors interpreted the polypoid lesions as implantations from the blood stream.

Rast and associates (1945) encountered an instance with involvement of the epicardium by numerous grayish white nodules which microscopically were characteristic of Hodgkin's disease. Extensive involvement of the mediastinum was also present.

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Clinicopathologic Correlations

GORDON B. MYERS

CONGENITAL HEART DISEASE

Coarctation of Aorta is often asymptomatic When complaints develop, they are usually referable to either (1) intracranial hypertension (throbbing headache, dizziness), or (2) ischemia of lower extremities (numbness, coldness, intermittent claudication on walking, delayed wound-healing). Left ventricular hypertrophy eventually becomes evident on physical, roentgen or electrocardiographic examination. The proximal aorta is dilated, causing a pronounced pulsation at the episternal notch. A systolic murmur maximal in the left upper interscapular area is a common finding, probably arising from the turbulence in the vicinity of the coarctation The presence of a stenotic lesion distal to the origin of the left subclavian artery is revealed by the following objective signs. The radial pulses are forceful, the strength of the right often exceeding that of the left, the femoral pulses are either impalpable or much weaker and somewhat later than the radials, due to the circuitous course of the blood The brachial systolic pressure is abnormally elevated; the femoral pressure is significantly lower and may be subnormal. Diastolic pressures are usually slightly to moderately elevated, but comparable in the four extremities, reflecting a uniform increase in peripheral resistance.

Collateral arterial circulation develops through anastomoses between the superior intercostal, scapular and internal mammary branches of the subclavian arteries and the intercostal branches of the descending aorta and between the internal mammary and epigastric arteries. The dilated tortuous intercostal arteries are manifested by (1) visible or palpable pulsations, or by localized systolic murmurs; and (2) roentgenographic evidence of erosion of the lower margins of the ribs.

Complications. Rupture of the dilated aorta is an important cause of death The long-standing hypertension may eventuate in cerebral hemorrhage or congestive failure. Subacute bacterial endocarditis may be engrafted on the commonly associated anomaly of bicuspid aortic valve or a comparable bacterial aortitis may occur at the site of coarctation.

Patent Ductus Arteriosus is asymptomatic when the shunt is small. Exertional dyspnea, palpitation and eventual congestive failure result from large shunts. Stunting of growth may also occur when the shunt is massive. Hoarseness is a rare complaint, referable to pressure of the dilated pulmonary artery on the recurrent *laryngeal nerve. Chronic cyanosis* and clubbing are absent, because the blood flows from aorta to pulmonary trunk.

The diagnosis is based on the demonstration of a continuous harsh machinery murmur, maximal in the second interspace to the left of the sternum, transmitted to the left clavicle and interscapular area, accompanied by a systolic or continuous thrill over the dilated pulmonary trunk. The murmur is accentuated late in systole and tends to envelop a loud pulmonic second sound. The continuity of the murmur from systole into diastole merely reflects uninterrupted blood flow from aorta into the pulmonary trunk. The diastolic portion of the murmur is absent in infancy because of lack of sufficient pressure-gradient between the aorta and pulmonary trunk, and may be absent in older children and adults if the shunt is small. Under these circumcumstances, exercise may increase blood flow and pressure-gradient sufficiently to convert a systolic into a continuous murmur.

The size of the heart depends upon the magnitude of the shunt. Since a large ductus may shunt 50 to 75 per cent of the blood expelled by the left ventricle, a twofold to fourfold increase in left ventricular output must be maintained for an adequate systemic circulation. This leads to left ventricular dilatation and hypertrophy. The excessive inflow into the pulmonary trunk causes dilatation, manifested by widening of area of percussion dullness and roentgen borders in the left second and third interspaces and by abnormally prominent pulsations in this area. When high pulmonary arterial pressures are maintained by a large shunt, right ventricular hypertrophy may eventually develop. The oxygen content of blood obtained from the pulmonary trunk by catheterization is significantly higher than that obtained from the right ventricle, because of influx from the aorta

Peripheral signs, like those of aortic insufficiency, are present at rest, if the ductus is large. These signs may be absent at rest, but demonstrable after exercise, if the ductus is small. The high pulse pressure and water-hammer pulse are an expression of elevation of the systolic pressure associated with the increased left ventricular output, together with precipitous drop in diastolic pressure resulting from the escape of considerable blood from the systemic circuit.

Subacute bacterial endarteritis is the commonest complication.` Since vegetations are prone to develop in the pulmonary trunk at the point of impingement of the stream from the ductus, emboli are released into the lesser circulation.

Patent Interatrial Septum. Cyanosis is likely to be present at birth because of persistence of the right-to-left shunt from fetal life, but disappears promptly after establishment of the normal pressure relationships in the two sides of the heart. Clubbing does not develop and cyanosis is absent during most of the life span because the pressure is greater in the left than in the right atrium and the blood consequently flows from left to right. Brief attacks of cyanosis may result from transitory reversal of shunt, precipitated by sudden rise of intrapulmonary pressure during coughing or straining; more prolonged cyanosis accompanies congestive failure. Stunting of growth is a consequence of large defects.

Dilatation and hypertrophy of the right atrium and ventricle. The blood shunted from left to right atrium, added to that coming from the vena cava, causes overfilling of the right atrium and ventricle, resulting in dilatation and hypertrophy of both chambers. Right ventricular hypertrophy causes abnormal systolic lifting of the sternum and adjoining fourth and fifth costal cartilages on the left When right ventricular hypertrophy develops early in life, it may give rise to a chest deformity characterized by protrusion of the lower sternum and adjacent left precordium. The right ventricular hypertrophy usually produces diagnostic signs in leads V_{3R}, V_1 and HV_1 characterized by either a late R wave preceded by a small Q wave or a late R′ wave preceded by a small brief R wave, or by small brief R and S waves, a late intrinsicoid deflection with little or no S or S′ wave, a depressed RS-T segment and a sharply inverted T wave The right atrial hypertrophy may be manifested in the same leads by P waves 3 mm. or more in amplitude and 0 12 second or longer in duration, and is frequently complicated by atrial (auricular) fibrillation *Mural thrombosis* is prone to occur in the dilated right atrium and constitutes a source for pulmonary embolism. Pulmonary infarction or pneumonia may precipitate right heart failure and thereby alter pressure relationships so that subsequent emboli pass through the septal defect into the systemic circuit.

Dilatation of the pulmonary trunk is a consistent finding produced by the increased right ventricular output and is recognized at the bedside by an abnormally forceful and extensive pulsation in the second and third interspaces to the left of the sternum. The pulsation is accompanied by a harsh systolic murmur and often by a systolic thrill and is followed by a diastolic shock and markedly accentuated pulmonary second sound. The dilatation may reach aneurysmal proportions and may be complicated by relative insufficiency of the pulmonary valve, manifested by a blowing diastolic murmur in the second and third interspaces along the left sternal border. Hoarseness may be produced by pressure on the recurrent laryngeal nerve. The pulmonary conus is abnormally prominent in the roentgenogram and the dilated pulmonary arteries cause exaggerated comma-shaped hilar shadows that pulsate vigorously, producing the "hilar dance." The presence of a shunt from left to right atrium may be confirmed on cardiac catheterization by the demonstration of a significantly higher oxygen content in blood obtained from the right atrium than in blood obtained from the venae cavae Anomalous entrance of a pulmonary vein into the right atrium and patent interatrial septum produce similar physiologic and clinical changes, but may be distinguished by angiocardiographic visualization.

Mitral stenosis is a common associated lesion and is usually rheumatic in etiology, but is occasionally the result of a congenital defect. The obstruction at the mitral orifice raises the left atrial pressure and thus favors shunting of blood into the

right atrium. The combination of mitral stenosis and atrial septal defect (Lutembacher's syndrome) produces greater right ventricular hypertrophy and greater dilatation of the pulmonary trunk than either lesion by itself and hence should be suspected in every case with exaggerated findings. The mitral stenosis is manifested by a rumbling diastolic murmur at the apex, best heard in the left lateral position, immediately after exercise, and is distinguished from uncomplicated mitral stenosis by the absence of the expected left atrial dilatation.

Patent Interventricular Septum is asymptomatic when it occurs as an isolated defect Cyanosis and clubbing are absent, since blood is always shunted from the left to the right ventricle The shunt is usually too small to affect cardiac size or function, a large defect may eventually produce right ventricular dilatation and hypertrophy and dilatation of the pulmonary trunk. The lesion is manifested by a long, harsh systolic murmur and usually by an associated thrill maximal in the third and fourth interspaces at the left sternal border. The murmur is transmitted widely over the precordium and into the interscapular area, but *not into the neck. The* diagnosis may be verified by demonstration of a significantly higher oxygen content in blood obtained from the right ventricle than in blood from the right atrium In some cases, there is an associated complete atrioventricular block, because of interruption of the bundle of His at the septal defect. Bacterial endocarditis is the commonest complication Since the vegetations are prone to develop at the point where the cross-stream strikes the right ventricular wall, emboli are dislodged into the lesser circulation to produce pulmonary infarction.

Tetralogy of Fallot. *Cyanosis and marked clubbing* of fingers and toes constitute the most striking features. The cyanosis is caused primarily by shunting of unoxygenated blood from the right ventricle into an overriding aorta and into the left ventricle through a patent interventricular septum, it is intensified by a complicating polycythemia, secondary to chronic arterial oxygen-unsaturation. Cyanosis rapidly deepens during exercise, as a result of fall in arterial oxygen saturation and fall in oxygen consumption per liter of air ventilated through the lungs. Hyperpnea increases progressively during exertion, because of increasing tissue anoxia and rising level of blood lactate, and dyspnea and fatigue soon necessitate termination of exercise The squatting or knee-chest position affords the greatest respiratory comfort, but orthopnea is absent. Stunting of growth is a common sequela of chronic anoxia. Dizziness, syncope, epileptiform convulsions, and focal cerebral manifestations may occur as a result of cerebral anoxia or thrombosis secondary to polycythemia.

The heart often appears normal in size on percussion and in the six-foot roentgenogram. Underlying right ventricular hypertrophy is usually manifested by abnormal systolic lifting of the sternum and *of the adjoining fourth and fifth* costal cartilages, occasionally by a protruding deformity of this portion of the chest, and almost always by diagnostic patterns in leads V_{3R} and V_1 similar to those described under patent interatrial septum.

The pulmonary trunk is usually small but may show post-stenotic dilatation. In childhood the hilar shadows are light and the lungs exceptionally radiolucent, but with advancing age the vascular shadows become more prominent as collateral circulation increases. The classical signs of pulmonary stenosis consist in a harsh systolic murmur with associated thrill in the second and third interspaces at the left sternal border, followed by a muffled, but pure, second sound, the thrill, how-

ever is often absent, the murmur is frequently soft and occasionally absent, because of markedly reduced flow through a high-grade stenosis. A loud, but unreduplicated, second sound of aortic origin may be maximal in the pulmonary area when the aorta is displaced to the left A right aortic arch is present in 25 per cent of the cases and is recognized by indentation of the right edge of the esophagus and by displacement of this structure towards the left.

Cardiac catheterization establishes the diagnosis of pulmonary stenosis by demonstrating an elevated pressure in the right ventricle but a significantly lower pressure in the pulmonary trunk Arm-to-tongue circulation time is shortened, owing to the right-to-left shunt.

Eisenmenger's Complex exhibits two of the features of tetralogy of Fallot, namely, dextroposition of the aorta and high ventricular septal defect, but is distinguished by the absence of pulmonary stenosis and the presence of a dilated or normal pulmonary trunk with normal pulmonary blood flow. Cyanosis develops in later childhood and gradually deepens, it cannot be fully accounted for by the degree of right-to-left shunt and is probably caused, in part, by progressive pulmonary vascular disease. The latter is accompanied by increasing pulmonary hypertension, which often gives rise to gross hemoptysis. Both right and left ventricular hypertrophy may be demonstrable clinically. A harsh systolic murmur and thrill are usually present at the base and may originate in either the dilated pulmonary trunk or dextroposed aorta, and the systolic murmur is often followed by a diastolic murmur along the left sternal border, resulting from pulmonary and, or, aortic regurgitation. The hilar shadows are prominent and may exhibit increased pulsations.

MYOCARDIAL DILATATION AND HYPERTROPHY

Chronic Left Ventricular Dilatation and ***Hypertrophy*** *represent a response to a* chronically increased load The commonest cause is systemic hypertension, but other causes include certain valvular defects (aortic insufficiency, aortic stenosis, mitral insufficiency) and certain lesions requiring prolonged maintenance of high cardiac output (chronic hyperthyroidism, chronic anemia, and arteriovenous fistula, including not only the traumatic variety, but also those associated with osteitis deformans). As a sequel to localized myocardial injury or destruction, such as attends infarction or inflammation, compensatory hypertrophy of the uninjured myocardium develops even in the absence of *hypertension, valvular defects or other* factors that increase left ventricular load

Physical signs. Left ventricular dilatation *is recognizable at the bedside by displacement of the apical impulse outward beyond the left midclavicular line and* downward into the sixth interspace or lower Projection of the point of maximal intensity of the apical impulse more than 1 centimeter beyond the midclavicular line in the fifth interspace is most often caused by left ventricular dilatation, but may also be produced by right ventricular enlargement or mediastinal shift; the diagnosis is established by demonstration of associated left ventricular hypertrophy or by exclusion of the other causes in the course of the examination of the heart and lungs. Left ventricular hypertrophy is revealed clinically by a heaving apical impulse that lifts one or more ribs or causes a sustained and forceful protrusion of the soft tissues, which cannot be obliterated by the palpating hand. Left ventricular enlar[illegible] *of sufficient degree to dilate the*

is complicated by relative mitral insufficiency, manifested by a blowing apical systolic murmur that follows the first sound and is transmitted towards the axilla

Roentgen signs. Concentric left ventricular hypertrophy causes increased convexity of the lower portion of the left cardiac border in P-A projection. As the left ventricle enlarges, its lower border projects downward into closer apposition to the diaphragm, its dorsal border extends dorsally to fill the retrocardiac space, and finally its rounded lateral border bulges more and more towards the left.

Electrocardiographic signs. Left ventricular hypertrophy is manifested by QR complexes in leads V_5, V_6, V_7 and, or, V_8, characterized by (1) a small Q wave measuring 0.02 second or less from onset to nadir and amounting to less than 25 per cent of the amplitude of the succeeding upstroke, (2) a prominent R wave consuming 0 04 second or more from onset to peak and exceeding 25 mm. in amplitude; (3) a late intrinsocoid deflection, beginning more than 0.05 second after the onset of the QRS; (4) a depressed, upwardly convex RS-T segment, and (5) an inverted (or, less typically, a flat to diphasic) T wave. The interval elapsing between onset and peak of the R wave and the amplitude of this deflection provide rough indices of the time required and voltage developed during passage of the impulse from endocardial to epicardial surface of the subjacent wall; the thicker the myocardium, the longer time consumed in inscription of the ascending limb of the R wave and the greater the voltage developed.

Symptoms of left ventricular failure. Dyspnea, the earliest symptom, is usually gradual in onset and progressive in development, appearing first during exercise formerly tolerated without discomfort, then during lesser and lesser exertion, and finally at rest. Dyspnea is caused chiefly by pulmonary congestion, which makes the lungs more rigid and resistant to expansion, thereby increasing the muscular effort of inspiration. The lessened elasticity of the congested lungs interferes with deflation and leads to an increase of intrapleural pressure, which adds to the difficulty of expansion. As failure increases, dyspnea is intensified by the need for maintaining increased minute respiratory volume to combat tissue anoxia, to reduce acidosis from accumulation of lactic and carbonic acids, and to increase dispersal of heat. Orthopnea, or labored breathing on recumbency, of sufficient severity to impel assumption of the erect position, is a cardinal symptom of left ventricular failure. The development of dyspnea on change from sitting to recumbent position is traceable to several factors: (1) increased pulmonary congestion consequent upon shift of blood from abdomen to lung and upon rise of pulmonary venous pressure owing to the necessity of lifting blood 4 to 7 centimeters to reach the left atrium; (2) elevation of the diaphragm with reduction in vital capacity; and (3) cerebral venous engorgement. Paroxysmal nocturnal dyspnea is an acute attack of orthopnea, waking the patient after one to two hours of sleep. The background for the attack is chronic pulmonary congestion from left ventricular insufficiency; the events during sleep in the recumbent position that lead to the attack are progressive increase in pulmonary and bronchial congestion with complicating pulmonary edema, consequent upon transfer of blood and edema fluid from the systemic circuit to the lungs, the precipitating factors that suddenly augment pulmonary engorgement and edema and waken the patient in acute dyspnea include nightmares, muscular movements and paroxysms of cough. The shortness of breath persists for minutes to hours after assumption of the sitting position and is characteristically accompanied

by cough, expectoration of a pinkish, frothy edema-fluid and wheezing, resulting from bronchial congestion with spasm and secretion of mucus.

Cough is not only associated with paroxysms of nocturnal dyspnea but also tends to be provoked by other activities or conditions that produce dyspnea, such as exertion and recumbency. The circumstances that bring on cough point to pulmonary congestion, rather than primary bronchial or pulmonary disease, as the cause. Gross hemoptysis may result from pulmonary infarction or from rupture of an engorged vessel.

Extracardiac signs of left ventricular failure. Pulmonary congestion and edema constitute the chief manifestations. The earliest evidence is obtained roentgenographically and consists in accentuation of hilar shadows and fan-like radiation towards the periphery at the bases; later, crackling râles are detectable at the bases and may be accompanied by sonorous and sibilant râles because of the presence of bronchial mucus and spasm. During acute pulmonary edema associated with a severe paroxysm of nocturnal dyspnea, moist and dry râles may be audible throughout both lungs Hydrothorax may occur more often on the left side, in the presence of isolated left ventricular failure, but becomes predominantly right-sided with coexistent right ventricular failure Pulmonary emphysema develops after long-standing congestion, as a result of loss of elasticity.

Cardiac signs. Left ventricular enlargement is invariably present and tends to increase with the advent of failure. Protodiastolic gallop rhythm is often audible at the apex in left ventricular failure. The third sound is the result of increased intra-atrial pressure, causing a more forcible opening of the mitral valve and inrush of blood into a dilated left ventricle. Accentuation of the pulmonic second sound occurs as a result of pulmonary hypertension. Tachycardia is present even though the patient is at physical and mental rest. Pulsus alternans, characterized by regularly spaced beats that alternate in force as judged by systolic pressure and pulse volume, is an ominous sign.

Circulatory tests. Circulation time from arm to tongue is prolonged because of stasis in the lungs and systemic circuit. Arm-to-lung time and venous pressure are within normal limits in the absence of right ventricular failure. Vital capacity is reduced.

Acute Left Ventricular Dilatation may be precipitated in persons with previously normal hearts by an acute myocardial lesion of ischemic, inflammatory or toxic origin, particularly when accompanied by an abrupt increase in cardiac work consequent upon acute hypertension, a valvular rupture, or rapid intravenous administration of excessive saline or hypertonic solutions. The frequent discrepancies between the degree of dilatation and the extent and severity of the histologically demonstrable lesion may be explained by one or more of the following factors: glycogen content, electrolyte partition, and oxygen supply. The signs of left ventricular dilatation and complicating failure have been described above.

Chronic Right Ventricular Dilatation and Hypertrophy are most commonly secondary to left ventricular failure, but may occur as the primary or major ventricular conditions under the following circumstances: (1) chronic cor pulmonale secondary to obstructive emphysema, extensive pulmonary fibrosis, or rarely diffuse pulmonary arterial obstruction from sclerosis or thrombo-embolism; (2) valvular defects, such as marked mitral stenosis, pulmonary stenosis and insufficiency; and (3) increased return flow to the right ventricle, resulting from large interatrial or interventricular septal defects and acquired arterio-venous fistulae.

Physical signs. The apical impulse may be displaced to the left of the midclavicular line and may exhibit systolic retraction of the soft tissues, if there is associated left ventricular atrophy, as in marked mitral stenosis. Systolic protrusion of the lower part of the sternum and the adjacent fifth, fourth and perhaps the third costal cartilages in a normal adult chest (but not in a flat chest) is indicative of right ventricular hypertrophy. Increased percussion dullness in the left third and right fourth interspaces may be found in right ventricular enlargement, but not in isolated left ventricular dilatation. Dilatation of the conus pulmonalis is manifested not only by percussion dullness in the third left interspace, but also by abnormal systolic pulsation and diastolic shock in the third and second interspaces, together with a systolic murmur and accentuated P_2. Evidence of tricuspid regurgitation may accompany enlargement sufficient to involve the inflow tract.

Roentgen signs. Enlargement of the right ventricle first takes place in a ventral direction and may be detectable in the left oblique position when the ventrodorsal (anteroposterior) diameter is normal. The first evidence in the anteroposterior (A-P) view consists in increased prominence of the pulmonary trunk and conus, due in part to rotation and in part to dilatation. With marked enlargement, the cardiac shadow is widened, both to the right and left.

Electrocardiographic signs. Right ventricular hypertrophy may produce diagnostic signs in leads V_{3R}, V_1, namely, either a prominent late R wave preceded by a small Q or a late R′ wave preceded by small brief R or S waves; a late intrinsicoid deflection with little or no S or S′ wave; and a sharply inverted T wave. Typically, lead V_6 shows a small R wave, early intrinsicoid deflection and prominent S wave. This pattern is the reverse of that associated with left ventricular hypertrophy. Other patterns sometimes associated with, but not pathognomonic of, right ventricular hypertrophy include complete and incomplete right bundle branch block.

Clinical manifestations of right ventricular failure. Right ventricular enlargement is an almost invariable forerunner. Protodiastolic gallop in the fourth and fifth interspaces at the left sternal border may appear with failure, but is less common than the analogous protodiastolic apical gallop associated with left ventricular failure.

Elevation of venous pressure is an early sign and is recognized at the bedside by distention of the cervical veins when the patient is in the sitting position. When relative tricuspid insufficiency occurs as a result of dilatation of the inflow tract of the right ventricle, the dilated cervical veins may exhibit pulsation during ventricular systole in place of the usual collapse.

Dependent subcutaneous edema appears about the ankles and lower portion of the legs, if the patient is ambulatory, and gravitates to the sacral region and dorsal aspect of the thighs, if he is bedridden; it may extend over the entire lower half of the body into the chest wall, but does not involve the face as long as orthopnea is present, since the latter demands maintenance of the sitting position. The edema represents a primary renal retention of sodium and a secondary retention of water and chloride, resulting from decreased glomerular filtration and increased tubular reabsorption. Increased output of antidiuretic hormone may also contribute to the oliguria and water retention. The accumulation of fluid in dependent parts is the result of the influence of elevated venous pressure and the consequent increase in capillary hydrostatic pressure on edema formation. Differences in tissue pressure also affect distribution of edema and account for massive accumulation in lax tis-

sues and the paucity in nearby areas where the skin is more firmly attached to the underlying fascia. Other factors which may contribute to cardiac edema include reduction in colloidal osmotic pressure from albuminuria, reduced protein intake and synthesis, increased capillary permeability secondary to anoxia; and impaired lymphatic drainage consequent upon elevation in venous pressure.

Enlargement of the liver is an early and often a persistent manifestation. During acute right heart failure there is progressive descent of the liver, accompanied by pain, tenderness and voluntary spasm in the right upper quadrant; during recovery there is gradual recession towards the costal margin Chronic right heart failure is accompanied by a persistently enlarged, firm, nontender liver The application of pressure to a passively congested liver causes increased dilatation of the cervical veins, because of the inability of the failing right heart to accommodate the increased return flow, whereas a similar maneuver in other forms of hepatomegaly has no effect on cervical venous pressure Impairment of hepatic function is usually demonstrable in patients with congestive failure and is attributable to anoxia, secondary to reduced hepatic blood flow and stasis. Jaundice is an occasional finding in patients with uncomplicated congestive hepatomegaly, but is likely to appear after pulmonary infarction, because of increased hepatic anoxia together with an excessive load of bilirubin. Anorexia and flatulence are common complaints referable to passive congestion of the gastrointestinal tract, and nausea and vomiting may accompany untreated congestive failure, as well as overdigitalization Acute abdominal pain accompanied by blood in the stools and shock, clinically resembling mesenteric thrombosis, is a rare terminal event and may result from extreme engorgement of the gastrointestinal tract without demonstrable arterial or venous occlusion. Ascites may complicate passive congestion of the liver and gastrointestinal tract, but is less pronounced than subcutaneous edema, except when the right heart failure is caused by constrictive pericarditis or tricuspid insufficiency.

Dyspnea generally continues in lessened degree when right heart failure complicates left failure and is no longer so likely to occur in nocturnal paroxysms because there is a reduction in pulmonary congestion, secondary to stasis in the systemic circuit. Shortness of breath, on the other hand, may persist or increase in some cases, as a result of accumulation of fluid in the pleural cavities Hydrothorax is more common in combined left and right failure than in uncomplicated left failure, owing to interference with drainage through both the azygos and pulmonary veins, but does not accompany isolated right failure with normal pulmonary venous circulation. Hydrothorax associated with combined left and right failure is characteristically bilateral, but more marked on the right because of the greater tendency of patients to lie on their right side.

Cyanosis is an almost invariable manifestation and tends to increase when right-sided failure supervenes on left, because of peripheral stasis which permits increased deoxygenation of blood. Phlebothrombosis in the femoral vein or its tributaries is a common and important complication of peripheral stasis and may, in turn, lead to pulmonary embolism

Circulatory tests Arm-to-lung time and arm-to-tongue time are prolonged. Venous pressure is elevated.

Acute Cor Pulmonale is produced by massive pulmonary embolism, rarely by massive pulmonary collapse, or by rupture of an aortic aneurysm into the pulmonary trunk Death may occur within a few minutes from cerebral or myocardial anoxia or secondary ventricular fibrillation,

it may occur hours later from right heart failure. In fatal cases of pulmonary embolism, there is only a rough correlation between the severity of the clinical picture, the length of survival, and the percentage of the pulmonary arterial tree found occluded at autopsy. Although embolic occlusion of more than 50 per cent of the pulmonary arterial bed is usually found in fatal cases, death may occur from smaller emboli, not only in debilitated, but also in robust persons, perhaps because of widespread reflex constriction of the coronary arteries and the nonembolized branches of the pulmonary arteries. The clinical picture of massive pulmonary embolism is dramatic in onset and is usually characterized by sudden severe dyspnea, acute retrosternal oppression and/or stabbing pleural pain, intense cyanosis, sudden weakness, dizziness, syncope or circulatory collapse. Shock may dominate the clinical picture and may obscure both dyspnea and chest pain. The objective signs may be classified into the following three groups:

Signs of pulmonary arterial obstruction During the first few hours after a single large embolus, there is marked cyanosis, intense air hunger with rapid shallow breathing, but little or no abnormality to percussion, auscultation or roentgen examination of the lungs. Within 12 to 24 hours, cough, hemoptysis and pleural pain may appear and pulmonary infarction may be demonstrable as an area of consolidation, accompanied by fever and leukocytosis and resembling pneumonia. A hemorrhagic pleural effusion develops in some cases and jaundice may occur, especially if right heart failure is present.

Signs of right ventricular dilatation and failure. Rapid dilatation of the pulmonary trunk, conus and right ventricle may be demonstrable on physical or roentgen examination. The dilatation of the pulmonary trunk and conus is manifested by the following signs in the second and third interspaces at the left sternal border: a pronounced systolic pulsation, sometimes accompanied by a thrill; a loud, rough systolic murmur and sometimes a superficial grating sound, due to impingement of the conus on the anterior chest wall; and a palpably and audibly accentuated pulmonic second sound. The physical signs of right ventricular dilatation and failure have been described above. Acute right ventricular dilatation and ischemia may be manifested electrocardiographically by (1) transient right bundle branch block, (2) displacement of the precordial transitional zone to the left, and (3) rapidly developing and receding cove inversion of the T waves in the first three or four precordial leads. These T wave patterns are distinguished from those associated with anteroseptal infarction by the fact that they are maximal in lead V_1 or V_2 and usually confined to leads over the right ventricle, by their more rapid evolution and by the absence of abnormal QR deflections.

Signs of systemic circulatory collapse or shock result from drastic reduction in left ventricular output, consequent upon obstruction to blood flow through the lungs. The pulse is rapid and thready, the blood pressure low, and the skin an ashen gray or lavender hue. Syncope, coma or focal signs of cerebral anoxia may be present.

ENDOCRINE, NUTRITIONAL AND METABOLIC MYOCARDIOPATHIES

Acromegaly is accompanied by marked cardiac hypertrophy, predominantly left ventricular, which is due in part to excess growth hormone, in part to associated hypertension. Coronary sclerosis is a frequent complication.

Cushing's Syndrome and Pheochromocytoma may be accompanied by left ventricular hypertrophy because of hypertension

Addison's Disease. In untreated cases, the heart is small, the blood pressure low. During crisis, electrocardiographic signs of hyperpotassemia may be present Plasma potassium levels between 7 and 9 mEq. per liter are accompanied by church-steeple configuration of the T waves (increased amplitude, narrowing of base and sharpening of apex) and sometimes by a lengthening of the QRS interval due to the appearance of a slurred S wave. Progressive rise in plasma potassium above 9 mEq./L. is marked by loss of P waves, and progressive broadening of the QRS, ending in a smooth biphasic QRS-T complex. Overtreatment with desoxycorticosterone leads to cardiac dilatation and failure with electrocardiographic signs of hypopotassemia, namely, depression of the RS-T junctions with flattening or inversion of the T waves and lengthening of the Q-T interval

Hyperthyroidism increases basal oxygen requirements by 25 to 100 per cent, thereby necessitating a corresponding increase in cardiac output. In patients with coexisting heart disease, the increased cardiac work imposed by hyperthyroidism causes increased hypertrophy and may precipitate failure. In most patients with uncomplicated hyperthyroidism, the heart is physiologically hyperactive, but anatomically normal, long-standing hyperthyroidism may, however, eventually lead to moderate cardiac hypertrophy, but very rarely causes failure, in the absence of other forms of heart disease

The classical thyrotoxic cardiovascular symptoms and signs may occur in the presence of an anatomically normal heart and are referable to physiologic cardiac hyperactivity and to peripheral vasodilatation. Thus, the typical apical impulse is a diffuse, slapping, staccato movement caused by hyperactivity, and differs from the heaving impulse of left ventricular hypertrophy in its rapid rise and immediate fall and in the ease of obliteration by the palpating hand. Despite the diffuseness of the apical impulse, the heart is characteristically normal in size to both physical and roentgen examination A sharp, snapping apical first sound and a sinus tachycardia at rest are other typical features of physiologic hyperactivity A systolic murmur is usually audible in the second and third interspaces at the left sternal border, because of dilatation of the pulmonary trunk, and a separate functional systolic murmur may be produced at the apex as a result of accelerated blood flow Atrial fibrillation, paroxysmal or persistent, is a common complication of chronic hyperthyroidism in the older age group Elevation in pulse pressure, owing to a rise in systolic in the presence of a normal or low diastolic pressure, is a common manifestation of increased cardiac output with peripheral vasodilatation and may be marked enough to give rise to a typical Corrigan pulse. Shortening of the circulation time is another classical feature The electrocardiogram is not diagnostic.

Myxedema. The cardiac borders are widened to left and right on percussion and roentgen examination, the widening may be due to cardiac enlargement from myxedematous infiltration and, or, to pericardial effusion. The apical impulse is usually imperceptible on physical examination and feeble on fluoroscopy. The heart sounds are faint and distant The pulse is characteristically slow and small in volume, reflecting the reduction in cardiac output, consequent upon diminished oxygen consumption Effusions of high protein content may occur into the subcutaneous tissue and into the pleural and peritoneal cavities, as well as into the pericardium, because of increased capillary permeability. The classical electro

cardiographic signs consist in low voltage of P and QRS complexes and flattening or shallow inversion of the T waves, and may be largely due to either the pericardial effusion or the myocardial lesion. Advanced sclerosis is a common complication of myxedema, but may be clinically asymptomatic until after the institution of treatment. Thyroid extract in proper doses causes (1) gradual return of the cardiac silhouette to normal (owing to absorption of pericardial effusion and, or, disappearance of cardiac dilatation); (2) concomitant improvement in the force of cardiac contractions and pulse volume; (3) gradual absorption of subcutaneous and serous effusion, and (4) increase in voltage of P and QRS complexes and change to upright T waves. Thyroid extract, particularly when given in large doses to myxedematous patients with coronary sclerosis, may precipitate angina pectoris or myocardial infarction, as the result of too abrupt an increase in demands upon the heart.

Beriberi. The underlying metabolic defect is a decrease in capacity to oxidize pyruvate and lactate, as a result of thiamin deficiency, the underlying physiologic change is peripheral arteriolar dilatation, perhaps secondary to accumulation of acid metabolites. Edema of the legs is often the initial symptom and may be due in part to hypoproteinemia; dyspnea is often abrupt in onset and usually becomes severe in degree. Multiple neuropathy, if present, is mild, as severe incapacitating grades tend to protect against cardiac failure through limitation of activity. The effect of widespread arteriolar dilatation is like that of a large arteriovenous fistula in accelerating blood flow through the tissues, in augmenting return flow to the right ventricle, and in imposing demands upon the left ventricle for increased output; hence, the classical syndrome of right and left ventricular dilatation, high pulse pressure, Corrigan pulse, and shortened circulation time. The combination of dilatation of the atrioventricular orifices and great vessels with increased velocity of blood flow results in loud harsh systolic murmurs at apex and base and sometimes in a diastolic murmur along the sternal border, and the condition may be mistaken for organic aortic insufficiency. The diagnosis is established by the specific response to large doses of thiamine, characterized by restoration of compensation, disappearance of murmurs and peripheral signs, and return of cardiac size to normal.

CIRCULATORY DISEASES

Coronary Sclerosis and Thrombosis are pathologic rather than clinical entities, diagnosable during life by inference based upon clinical findings produced by myocardial infarction or ischemia. Thus, the symptoms, physical and electrocardiographic signs of the syndrome often designated clinically by the term "coronary thrombosis" may be correlated with myocardial infarction, but not directly with coronary thrombosis. This symptom complex accompanies myocardial infarction, irrespective of the presence or absence of underlying coronary occlusion. On the other hand, when localized coronary narrowing is sufficiently gradual in development to permit the establishment of an adequate collateral circulation, an occlusion may cause no demonstrable clinical manifestations or pathologic changes in the myocardium. Moreover, the symptom complex of angina pectoris and the accompanying electrocardiographic changes often ascribed to "coronary sclerosis" are

referable to acute myocardial ischemia rather than to the alterations in the walls of the coronary vessels *per se*. Hence, correlations will be made between the clinical manifestations and the myocardial rather than the coronary lesion.

Acute Myocardial Infarction may occur without warning, particularly when associated with sudden thrombosis of a previously sclerotic but patent coronary artery, or may be preceded by significant premonitory symptoms, especially when there is rapidly progressive coronary narrowing sufficient to cause myocardial ischemia, prior to actual infarction. Thus the sudden development of angina pectoris or an abrupt increase in frequency and duration of preexistent angina may herald an impending infarction. The infarct may be precipitated by a sudden increase in the demands upon an ischemic myocardium imposed by exercise or excitement or it may occur during rest, as a result of further reduction in blood supply by thrombosis.

Clinical Manifestations

Pain is an expression of acute myocardial anoxia, as indicated clinically by its mode of onset and its constrictive, viselike character, and confirmed pathologically by the invariable demonstration of anoxic lesions. The pain impulses are carried to the first to fourth thoracic segments by way of sympathetic afferents and are usually referred over the somatic connections of the same segments to account for the retrosternal location and radiation into the medial aspect of the arm, but may spread to cervical segments, resulting in a choking sensation in the neck, or to lower thoracic segments, resulting in epigastric or upper abdominal pain. In the latter event, the location of the pain, together with the commonly associated epigastric distention, nausea and vomiting, may lead to an erroneous diagnosis of an acute surgical abdomen. The prolonged duration of the pain and the failure of vasodilating agents, such as nitroglycerine, are a reflection of the presence of severe and often irreversible anoxic degeneration; the pain eventually subsides spontaneously when the anoxic fibers undergo necrosis or recovery. The pain is submerged in some cases by overwhelming dyspnea or shock, or it may be absent if the nervous pathways are interrupted.

Sudden weakness and faintness are common complaints, a rapid pulse of small volume, lowering of systolic and pulse pressures, and cold clammy extremities are generally demonstrable as manifestations of reduced left ventricular output. Profound shock due to marked fall in cardiac output may dominate the clinical picture, syncope or coma may result from transitory or prolonged cerebral ischemia.

Sudden dyspnea results from acute pulmonary congestion associated with failure of the infarcted left ventricle and may constitute the major complaint or may be subordinate to pain or shock. In the former event, cough productive of copious pinkish, frothy sputum is often present and signs of diffuse pulmonary edema and bronchospasm are present (page 921); in the latter event, crackling râles are demonstrable, at least at the lung bases. Acute pulmonary congestion throws a sudden load upon the right ventricle and may be followed by hepatic engorgement and elevation of systemic venous pressure. Acute pulmonary congestion is especially prone to precipitate right ventricular failure in patients with antecedent infarction or left ventricular failure.

Cardiac examination usually reveals enlargement (due to antecedent left ventricular disease and, or, acute dilatation) and often discloses evidence of left ventricular failure (softening of the apical first sound in the presence of a normal second sound, protodiastolic gallop, accentuation of the

pulmonic second sound). Pericardial friction rub is likely to be heard when there is an extensive fibrinous reaction, but is often not detectable when pericarditis is well localized *Arrhythmias:* Premature systoles are prone to arise from injured muscle near the boundaries of the infarct and when frequent or multifocal constitute a forerunner of ventricular tachycardia and/or fibrillation. Atrioventricular block may complicate acute posteroseptal infarction, but usually disappears during convalescence Atrial fibrillation is a fairly common, usually transitory complication and should lead to search for evidence of atrial infarction, but may occur as a complication of infarction limited to the ventricles

Fever, leukocytosis and elevation of sedimentation rate are manifestations of acute infarction and may be utilized as indices of the size of the infarct, provided other causes are excluded.

Complications and sequelae. Systemic embolism may occur as a result of detachment of a mural thrombus arising from the endocardial surface of a left ventricular infarct Pulmonary embolism is a common complication, generally originating from a phlebothrombosis in the lower extremities. Congestive failure, present during the acute stage, may prove therapeutically refractory or congestive failure may return or appear for the first time during convalescence Rupture of the outer wall of the heart is a common cause of sudden death during the first three weeks. Rupture of the interventricular septum may be survived temporarily and is recognized by the appearance of a loud, rough systolic murmur and accompanying thrill, maximal in the fourth or fifth interspace near the left sternal border *Ventricular aneurysm.* During the acute stage, the non-contractile infarcted myocardium tends to balloon out under the stress of the systolic intraventricular pressure; as the lesion heals by fibrous tissue replacement, the scar may continue to bulge, forming a permanent ventricular aneurysm. Systolic protrusion of an aneurysm of the anterior wall of the left ventricle may be manifested by an extensive impulse that lifts ribs or resists obliteration by the palpating hand. Fluoroscopic examination may reveal bulging and paradoxic systolic protrusion of a portion of the left ventricular wall. Shoulder-hand syndrome, consisting of (1) periarthritis of the left shoulder, manifested by pain, stiffness, and limitation of joint motion; and (2) dystrophy of the left hand, manifested by pain, stiffness and swelling, may develop during convalescence, because of a combination of reflex muscular spasm, disuse and in some cases vasoconstriction of sympathetic origin.

Electrocardiographic Findings

Tracings taken with an exploring electrode applied to the thoracic cage or esophagus, paired with the Wilson central terminal as an indifferent electrode, represent chiefly the potential variations of the epicardial surface subtended by the exploring electrode. A sufficient number of such semidirect leads to cover the surface of the heart will provide enough evidence, not only for the establishment or exclusion of recent infarction, but also for a rough estimate of the distribution of the lesion between endocardium and epicardium and its size and location with reference to the cardiac surface. Serial electrocardiograms will permit an estimate of the age of the infarct.

Electrocardiographic Estimation of the Distribution of an Infarct Between Endocardium and Epicardium is based chiefly on QRS configuration, but is sometimes aided by the RS-T pattern in leads from the left precordium, axilla, back, or from the lower esophagus, stomach or left leg. When the infarct is large, three concentric zones can be distinguished pathologically,

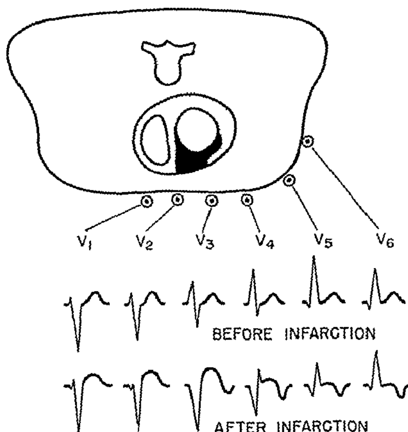


Figure XIII-1 Electrocardiographic findings in anterolateral apical infarction

and usually upon electrocardiographic examination as well: (1) a central zone of transmural infarction, extending through the entire wall from endocardium to epicardium, (2) a marginal zone of infarction confined to a portion of the wall, almost always the subendocardial layer, and (3) an outlying zone of ischemia, manifested by pallor and absence of histologic evidence of degeneration If the infarct is small, only the marginal and ischemic zones may be demonstrable

1 *Findings in leads subtending a central zone of transmural infarction* (Figure XIII-1, lead V_3). The registration of an abnormal QS complex in a lead facing the epicardial surface of the left ventricle, which should normally exhibit an R wave as the major deflection, constitutes evidence of transmural infarction of the underlying wall. If the entire thickness of the subjacent myocardium is dead, the QS deflection has smooth descending and ascending limbs and the T wave resembles that in leads facing the left ventricular cavity (aV_R) and remains fixed in serial tracings. In the event of islands of acutely injured but living muscle in the more superficial layers of the transmural infarct, the QS deflection is notched or slurred, the RS-T complex is at first markedly elevated and monophasic upright in contour and in subsequent serial tracings, the RS-T junction gradually approaches the isoelectric line, and the T waves undergo progressive cove-plane inversion. If the central zone is small, semidirect leads may fail to show a QS deflection, but instead may show an

abnormal QR complex referable to the surrounding marginal zone of subendocardial infarction.

2 *Findings in leads subtending a marginal zone of subendocardial infarction* (Figure XIII-1, leads V_{4-5}). Abnormal QR patterns in left ventricular leads, characterized by an initial downstroke 0 03 second or longer from onset to nadir and more than 25 per cent of the amplitude of the succeeding R wave, are diagnostic of subendocardial infarction and are recorded at the margins of a transmural infarct, because of the tendency for such lesions to extend further on their endocardial than on their epicardial surface. A rough estimate of the relative thickness of the infarcted subendocardial and living subepicardial layers may be made from the time of onset to nadir of the Q, as compared with the time from onset to peak of R and from the relative amplitudes of the Q and R waves The state of the living subepicardial layer is reflected in the RS-T segments and T waves. Acute injury to subepicardial muscle is manifested by elevation of the RS-T segment with monophasic upright T wave, subsidence of the injury to leave residual ischemia is accompanied by progressive return of the RS-T junction towards the isoelectric line, together with increasing cove-plane inversion of the T waves; decreasing ischemia and eventual recovery are marked by gradual decrease in the depth of the inverted T waves and eventual replacement by normal upright T waves. Preservation of the overlying subepicardial layer in acute subendocardial infarction permits registration of effects of acute subendocardial injury, namely, abnormal depression of the RS-T junction in overlying leads, with gradual return to the isoelectric line in serial tracings. In the rare cases where the marginal zone is characterized by infarction of the subepicardial layer and preservation of the *subendocardial* layer, the electrocardiographic findings resemble those of acute pericarditis (page 937).

3. *Findings in leads subtending an outlying zone of ischemia* (Figure XIII-1, lead V_6) are characterized by a normal QRS pattern, an isoelectric RS-T junction and cove-plane inversion of the T wave, with gradual return to normal erect T wave, as recovery occurs. Leads over the uninvolved wall opposite an infarct (Figure XIII-3, lead V_4) tend to show patterns reciprocal to those recorded in leads facing the infarct, namely, exaggeration of the R wave, initial depression of the RS-T junction and progressive return to the isoelectric line, together with increasing height of the erect T waves.

Electrocardiographic Localization of the Infarct *is based on the fact that* tracings obtained through Wilson chest leads represent chiefly the potential variations of the epicardial surface subtended by the exploring electrode, and is made by mapping out the anatomic relationship of leads showing abnormal QS or QR patterns to the surface of the heart. Satisfactory correlation between the electrocardiographic estimate of the size and position of the infarct and the pathologic findings can be achieved, provided a sufficient number of semidirect leads is available to cover the surface of the heart and to delineate the zones of reference of the potential variations of the two ventricles. The customary positions for application of the exploring electrode are as follows: V_1 in the fourth interspace at the right sternal border, V_2 in the fourth interspace at the left sternal border; V_3 midway between V_2 and V_4; V_4 in the fifth interspace in the left midclavicular line, $V_{5, 6, 7, 8, 9}$ at the same horizontal level as V_4, but in the vertical plane of the anterior axillary, mid-axillary, posterior axillary, scapular and paravertebral lines, respectively. Since positions $V_{4, 5, 6, 7}$ are at the level of the apex, exploration of the basal aspect of the left

ventricle requires additional high leads taken at the intersections of a horizontal line at the level of the junction of the third interspace and sternum with vertical lines through the V_3, V_4, V_5, V_6, V_7 and V_8 positions. A prerequisite to the interpretation of multiple chest leads consists in the delineation of the transitional zone between the two ventricles in the lower and upper precordium and preferably in the back as well

The transitional zone serves as an index of the projection of the ventral and dorsal ends of the septum onto the chest wall, and thus serves as a dividing line between the portion of the chest receiving predominantly the potential variations of the left ventricle and the portion receiving chiefly the potential variations of the right ventricle. When the transitional zone is in its usual position in the vicinity of lead V_3 anteriorly and near the mid-line posteriorly, the potential variations recorded through precordial leads at and to the left of the transitional zone (V_3 and V_4) come chiefly from the apical portion of the anterior wall of the left ventricle, those recorded through the usual axillary leads (V_5, V_6 and V_7) come mainly from the anterolateral, lateral and posterolateral aspects of the left apex, respectively, those recorded in back leads (V_8 and high V_8) and the low esophageal leads usually come chiefly from the posterior wall of the left ventricle, those in leads from the left leg (aVF), stomach and lower part of the back (below twelfth rib, but in the same vertical plane as $V_{7,\ 8,\ 9}$) come principally from the diaphragmatic surface. When the transitional zone is displaced to the left of the midclavicular line, as a result of dilatation of the right ventricle and, or, clockwise rotation of the heart, the potential variations of the anterior wall of the left ventricle are referred to the anterior axilla, those of the lateral wall to the posterior axilla. The following description of electrocardiographic abnormalities associated with the commoner sites of infarction is based on the assumption of normal cardiac position and would have to be modified, as described above, in the event of displacement of the transitional zone.

1. *Infarction of the antero-apical aspect of the left ventricle* Small infarcts limited to the apical third of the anterior wall of the left ventricle are manifested by abnormal QR patterns localized to leads V_3 and/or V_4. Larger infarcts involving the apical half or more usually extend transmurally through a sufficiently large area to be manifested by abnormal QS patterns in lead V_3 and, or, V_4 (Figure XIII-1). Continuation into the basal aspect of the anterior wall is indicated by abnormal QR patterns in high precordial leads. Such lesions almost invariably extend subendocardially into the apical third or more of the lateral wall, producing abnormal QR patterns in leads V_5 and V_6 and generally continue around the tip of the left ventricle into the posterior aspect of the apex Extensions limited to the apical third of the posterior wall are seldom recognizable in the usual chest and limb leads, extensions into the apical half or more of the posterior wall are generally manifested by abnormal QR patterns in lead aVF and in leads from the back below the diaphragm. Practically all large antero-apical infarcts continue into the adjacent interventricular septum and many produce QRS-T abnormalities in leads to the right of the septum (V_1 and V_2). A diagnostic pattern characterized by a QRS interval of 0.12 second or more, an abnormal Q wave and a prominent late R wave, an elevated RS-T segment or cove negative-T wave in right precordial leads may be correlated with transmural infarction of half or more of the septum A diagnostic pattern characterized by a QRS interval below 0.12 second, a small Q wave, a small R wave and deep S wave in right precordial leads (V_1

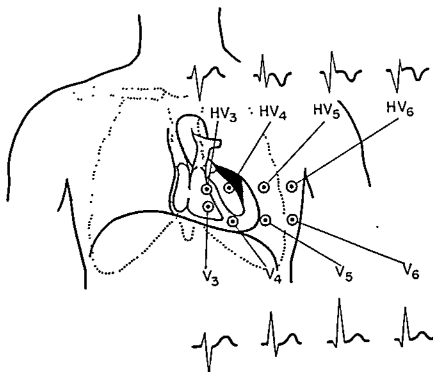


Figure XIII-2 Electrocardiographic findings in infarction of the base of the lateral wall of the left ventricle

and V_2 of Figure XIII-1) may be correlated with infarction of the left side of the septum. QS deflections accompanied by abnormal elevation of the RS-T segments in V_1 and V_2 may also be associated with septal infarction, but are not pathognomonic, unless accompanied by typical RS-T evolution in serial tracings. The occasional extension of large anterior infarcts across the septum into the adjacent anterior wall of the right ventricle does not produce localizing electrocardiographic signs.

2. *Infarction of the lateral wall of the left ventricle.* The commonest site in the lateral wall is the apical one-third, but most infarcts in this area are extensions of antero-apical lesions, some are continuations of high lateral infarcts, a few represent extensions of posterior infarcts, and a few are primary in the apical portion of the lateral wall. Infarction confined to this area may be manifested by abnormal QR patterns in leads V_5 and, or, V_6 only; infarction extending into this area from other portions of the heart is manifested by abnormal QRS patterns in additional leads, depending upon the distribution of the remainder of the lesion. The most common primary infarct of the lateral wall is bullet-shaped with base near the atrioventricular groove. Large infarcts of this type project sufficiently into the apical third of the lateral wall to produce abnormal QR patterns in V_5, V_6 and, or, V_7; smaller infarcts, largely confined to the basal half of the lateral wall, are not detectable in these leads. Signs suggestive of high lateral infarction are often demonstrable in lead aV_L, taken with the exploring electrode on the left arm, but the diagnosis is established by abnormal QR or QS patterns in high axillary leads (high V_5, V_6 and V_7), as exemplified by Figure XIII-2.

3. *Infarction of the posterior wall of the left ventricle* is more likely to be missed electrocardiographically than infarction of the anterior or lateral walls, because the posterior wall is less accessible to exploration by surface leads, yet more subject to

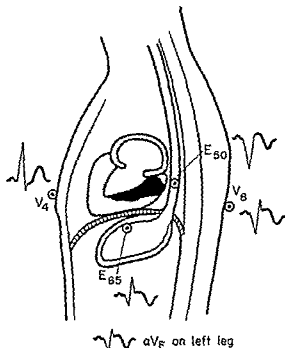


Figure XIII-3 Electrocardiographic findings in infarction of the posterior wall of the left ventricle

variations in anatomic relations, as a result of the influence of the height of the diaphragm. *A portion of the posterior wall of* one or both ventricles rests on the diaphragm, the remainder faces the posterior wall of the thorax. The major portion of *the diaphragmatic surface of the heart is* made up of the apical half of the posterior wall of the left ventricle when the diaphragm is low to normal *in position and* consists of right ventricle when the diaphragm is elevated. In the *former situations* (vertical to intermediate electrical position), the potential variations of the postero-apical aspect of the left ventricle have the predominant influence on leads from points below the diaphragm (left leg, low back and stomach (Figure XIII-3), whereas the potential variations of the posterobasal aspect of the left ventricle are referred mainly to lower esophageal and back leads V_8 and high V_8 (Figure XIII-3); in the latter situation (horizontal electrical position), the potential variations of the right side of the septum and posterior wall of the right ventricle are transmitted downwards to be recorded in subdiaphragmatic leads, while those of the *posterior wall of the left ventricle* are transmitted to mid-back and high-back leads. The most common primary infarct of the posterior wall takes the form of a truncated cone with base paralleling the atrioventricular groove

Smaller infarcts limited to the basal third of the posterior wall of the left ventricle may produce abnormal QR patterns in high V_{7-8}, in lower esophageal leads and perhaps in V_5, but not in low-back or left-leg leads. Larger infarcts extending through the middle third of the posterior wall will, in addition, be accompanied by abnormal QR patterns in lead aV_F and other subdiaphragmatic leads, provided that the heart is in vertical to intermediate position. On the other hand, if the heart is in horizontal position, large posterior *infarcts* may be undetectable in lead aV_F and in leads from stomach and *low back unless they extend sufficiently* into the septum to produce typical patterns of septal infarction (discussed above) in these leads Complete atrioventricular *block may accompany massive septal* extensions of posterobasal infarction. *Extension of massive infarcts across the septum into the posterior wall of the right* ventricle is fairly common, but does not significantly alter the electrocardiographic findings. Continuation of posterior infarcts into the basal portion of the lateral wall is manifested by abnormal QR patterns in high V_7 and high V_8; continuation into the apical portion of the lateral wall by diagnostic signs in customary V_7 and V_8 Infarcts involving the apical, but not the basal, portion of the posterior wall usually represent extensions of anterior infarction, but are seldom recognizable electrocardiographically unless they involve more than *the apical third of the posterior wall.*

4. *Atrial infarction* may be manifested by rapidly changing ectopic atrial rhythms, serial changes in contour of the P wave, or in the position or contour of the PQ segment.

***Electrocardiographic Estimation of the* Age of the Infarct** is based chiefly on a comparison of the RS-T pattern in serial tracings Recent infarction is manifested by progressive changes in RS-T segment and T waves; healed infarction by a fixed pattern in serial tracings. In recent infarction with acute subepicardial injury, the RS-T junctions show abnormal elevation that changes from day to day, increasing if injury spreads, receding towards the isoelectric line as it subsides, the T waves are at first monophasic upright, then show increasing inversion of their terminal portions. With the disappearance of acute injury, the RS-T junction becomes stabilized, usually at the isoelectric level, and as organization proceeds, the T waves at first show increasing cove plane inversion, then a much more gradual decrease in depth, *and finally may return to a normal upright* contour. Permanent fixed RS-T elevation and cove plane inversion of the T waves associated with abnormal QS or QR patterns occur with healed infarcts that involve a sufficiently large area of the wall to form ventricular aneurysms. The QRS pattern is of less help in determining age and often remains constant in serial tracings, even though the infarct is recent or organizing. However, significant changes in QRS pattern, found when adequate technical precautions are taken to insure against variations in electrode position, constitute evidence of activity. A definite increase in duration and amplitude of the Q wave at the expense of the R wave at a constant electrode position would indicate spread of an underlying subendocardial infarct towards the epicardium; change from normal QRS complexes at the boundaries of the lesion to abnormal QR deflections would indicate increase in area of infarction. On the other hand, abnormal QS and QR patterns found early in the stage of injury may show considerable increase in the R wave at the expense of the Q, *if a portion of the injured myocardium* recovers.

Angina Pectoris is a clinical syndrome, expressive of acute myocardial ischemia. Clinical and pathologic manifestations may be classified into two groups, namely, those referable to acute myocardial ischemia and those referable to the underlying disease.

Manifestations of acute myocardial ischemia Anginal pain is an expression of acute myocardial anoxia, as evidenced by (1) its strangling character; (2) its precipitation by factors that suddenly increase demands on the heart (such as exertion), by factors that in addition may cause reflex coronary constriction (such as intense emotion, gastric distention or cold) or by factors that abruptly reduce oxygen content of arterial blood (such as inhalation of a mixture of 10 per cent oxygen and 90 per cent nitrogen), (3) the prompt relief afforded by rest, by coronary dilators (such as nitroglycerine) or by inhalation of 100 per cent oxygen; and (4) the associated electrocardiographic changes.

Electrocardiograms taken during spontaneous or induced angina pectoris characteristically show acute RS-T depression of one millimeter or more, usually accompanied by flattening or reversal in the T wave in leads overlying the ischemic area (V_3-V_6) with involvement of the anterolateral aspect of the left apex, V_7-V_9 and aV_F with localization to the posterior wall, high axillary leads with ischemia high in the lateral wall. Repeat tracings after subsidence of the attack show prompt return to the pattern present before the onset of the attack. These electrocardiographic changes are referable to acute transitory injury to the subendocardial layer, as evi-

denced by the similarity to patterns produced in animals by mechanical, chemical or thermal injury confined to the subendocardial portion of the wall. Rarely, angina pectoris is accompanied by acute RS-T elevation in leads overlying the ischemic area, owing to subepicardial localization or transmural extension of the ischemia. QRS changes usually do not accompany brief attacks of angina pectoris unless the conduction system is involved, in which event transitory bundle branch block may be recorded.

Sudden death may occur during an attack from ventricular fibrillation or standstill If such a catastrophe should occur in a patient who had never had an attack of acute myocardial ischemia lasting more than fifteen minutes, pathologic examination might fail to show evidence of a myocardial lesion. In some cases, anginal pain and acute RS-T depression may last for one or more hours without clinical or electrocardiographic signs of gross infarction. This syndrome has been referred to as "coronary failure," in contradistinction to angina pectoris, on the one hand, and acute myocardial infarction, on the other. Should death occur during such an attack, pathologic examination reveals patchy myomalacia in the subendocardial layer, verifying the ischemic origin of the pain and the electrocardiographic localization of the ischemia in the subendocardial layer

Manifestations of the underlying disease. The background for most cases of angina pectoris is marked narrowing or occlusion of one or more branches of the coronary tree, due to arteriosclerosis, the underlying lesion in a minority is aortic valvular disease, either rheumatic or calcific aortic stenosis, or syphilitic aortic insufficiency with narrowing of the coronary ostia. Acute myocardial ischemia rarely occurs in the absence of significant coronary narrowing or aortic valvular disease, in such instances the ischemia may be traced to severe anemia from sudden massive blood loss, to marked arterial anoxemia from pulmonary or congenital heart disease, or to a combination of marked hyperthyroidism and tachycardia. Hence, clinical establishment of angina pectoris constitutes presumptive but not pathognomonic evidence of coronary disease.

Chronic Anemia is compensated, in part, through increase in cardiac output and acceleration of circulation time. To accomplish the excessive work in the face of reduced arterial oxygen content, dilatation and subsequent hypertrophy of both ventricles occur

Dilatation of the great vessels and/or the mitral and tricuspid rings, together with the accelerated blood flow, produces murmurs at one or more valvular orifices that may be mistaken for organic valvular disease The commonest manifestation is a systolic blowing murmur in the second and third interspaces along the left sternal border (the so-called hemic murmur), referable to dilatation of the conus and pulmonary trunk When dilatation is great enough to cause insufficiency of the pulmonary valve, the systolic murmur may be accompanied by a cavernous blowing diastolic murmur in the same area. Comparable systolic and diastolic murmurs may rarely occur in uncomplicated anemia as a result of dilatation of the aortic ring, the systolic murmur attaining maximal intensity in the second interspace at the right sternal border, the diastolic in the third and fourth interspaces along the left sternal border. A systolic murmur that is loudest at the apex and transmitted to the axilla is a common finding in chronic anemia and is referable to dilatation of the mitral ring. Occasionally a rumbling diastolic murmur, resembling that of mitral stenosis, may occur in the presence of anemia without organic mitral valvulitis Mitral and aortic diastolic murmurs are

more prone to occur in sickle cell anemia than in other etiologic types and may lead to an erroneous clinical diagnosis of rheumatic heart disease.

The electrocardiogram in severe anemia may show depression of the RS-T segments and inversion of the T waves. These findings resemble those associated with myocardial ischemia from other causes and may disappear after correction of the anemia.

INFLAMMATORY DISEASES

Acute and Subacute Pericarditis

Symptoms. Pain may result from irritation of the parietal pericardium of the anterior chest wall and diaphragm, or from contiguous pleurisy, but is absent in many cases, because the entire epicardium and much of the parietal pericardium are insensitive. Pericardial pain is generally dull and oppressive, but may be sharp and stabbing, it may be distributed diffusely over the precordium or may be confined to the retrosternal area, it may be referred to the left side of the neck and shoulder by way of the phrenic nerve or to the abdomen by way of the lower intercostal nerves Pain associated with pericarditis may simulate that of myocardial infarction or that of the acute surgical abdomen. Dyspnea varies with the size and rapidity of accumulation of the effusion and results chiefly from mechanical compression of the bronchial tree Dry hacking cough is a frequent symptom, probably of reflex origin.

Chest Signs depend upon the character and amount of exudate Fibrinous pericarditis is manifested by a superficial scratchy or leathery friction rub, usually audible in diastole as well as systole, but subject to variations in intensity and quality, occurring spontaneously or induced by modifications in pressure of the stethoscope. The friction rub may be evanescent or it may persist after development of effusion. Pericardial effusion may be distinguished from cardiac dilatation by the following physical signs: The apical impulse is either absent or faint and well within and above the percussion border in pericardial effusion, and is usually pronounced and adjacent to the left border of dullness in cardiac enlargement. The ratio of absolute to relative dullness is much greater in pericardial effusion, because of the tendency for the distended sac to displace the lung from contact with the ventral chest wall Abnormal dullness in the second interspace to the left of the sternum is detectable in recumbent patients with pericardial effusion, because of distention of the cephalic portion of the sac, but is not found in uncomplicated cardiac enlargement. The cardiac sounds are more muffled and distant in pericardial effusion and may be accompanied by a pericardial friction rub. Pericardial effusion may be accompanied by distinctive compression signs, namely, tamponade, to be described below, and Ewart's sign, consisting of dullness and bronchial breathing at the angle of the left scapula, resulting from compression atelectasis of the left lower lobe. The roentgen shadow assumes the shape of a water bottle when the patient is erect and becomes more globular upon recumbency. Fluoroscopy reveals diminished to absent pulsations due to the dampening effect of the fluid.

Cardiac tamponade results from elevation of intrapericardial pressure and consequent interference with diastolic filling The chief clinical manifestations are: (1) elevation in systemic venous pressure, as evidenced by enlargement of the liver and abnormally dilated but nonpulsatile cer-

vical veins; (2) shock with tachycardia and low pulse pressure secondary to reduced cardiac output; and (3) paradoxic pulse. Elevated intrapericardial pressure prevents the increase in venous return to the right heart, which normally compensates for the greater blood-containing capacity of the inflated lung. This uncompensated pooling causes left heart output and the pulse to fade during inspiration, to increase again on expiration as blood is forced from the deflating lung

Electrocardiographic Signs are referable to underlying subepicardial myocarditis The acute stage, or stage of injury, is characterized by elevation of the RS-T junctions with monophasic upright T waves in unipolar leads facing opposite ventricular surfaces and in the three standard leads The QRS complex may be reduced in voltage, but is not altered in contour As the lesion passes into the subacute phase, serial tracings reveal progressive return of the RS-T segments to the isoelectric line and increasing cove-plane inversion of the T waves in the same leads. With recovery, the electrocardiogram may return to normal.

Character of the pericardial fluid depends upon etiology Purulent effusions result from infections with pyogenic cocci, serofibrinous effusions are associated with rheumatic fever and tuberculosis, hemorrhagic effusions may occur in tuberculosis.

Chronic Pericarditis

Adhesive Pericarditis, resulting in obliteration of the pericardial cavity, and adhesive mediastinopericarditis, manifested by adhesions to the thoracic cage and surrounding mediastinal structures, may be asymptomatic, provided there is no interference with diastolic cardiac filling or constriction of the great veins. Adhesions between the obliterated pericardial sac and the thoracic cage may be detectable clinically by the traction phenomena. In place of the normal systolic apical protrusion, there is systolic retraction of the soft tissues at the apex and perhaps systolic retraction of the ribs and interspaces between apex and sternum, followed by a sharp diastolic rebound. The apex remains fixed when the patient shifts into the left lateral and right lateral positions. Systolic retraction of the tenth to twelfth ribs in the left dorsal portion of the chest wall (Broadbent's sign) may result from diaphragmatic adhesions, but may also be associated with marked cardiac enlargement in the absence of pericardial disease. Despite these traction phenomena, cardiac function may remain normal as long as there is no interference with diastolic filling

Constrictive Pericarditis limits diastolic ventricular relaxation and interferes with atrial and ventricular filling, thereby producing chronic cardiac tamponade. The chief complaint is generally referable to ascites with associated hepatic enlargement Dyspnea is usually present on exertion Peripheral edema is late in appearance and relatively mild in degree. Although the clinical picture is suggestive of cirrhosis, the correct diagnosis is revealed by marked dilatation of the cervical veins The elevation in venous pressure is more constant and more refractory to medication than that associated with myocardial failure and the dilated veins do not show the systolic pulsation usually present in congestive failure. Pulsus paradoxicus is almost invariable and the pulse pressure is low, owing to reduction in systolic pressure. A small quiet heart is the classical finding on physical and roentgen examination Pericardial calcification may be demonstrable. The apical impulse, when detectable, is manifested by systolic retraction instead of the usual outward thrust and tends to be fixed in position with change in posture. Other traction phenomena, described above, may be

present but are less common than in nonconstrictive mediastinopericarditis. In typical cases, the electrocardiogram reveals inverted T waves in all limb leads and in most precordial leads, associated with QRS complexes low in voltage, but normal in contour These changes are referable to involvement of the subepicardial portion of the myocardium. Atrial fibrillation is fairly common and is presumably the result of extension of the fibrosis into the atrial myocardium.

Endocarditis and Valvulitis

RHEUMATIC VALVULITIS

Active Rheumatic Valvulitis. During the course of acute rheumatic fever, changes in apical heart sounds may be produced by either acute mitral valvulitis, cardiac dilatation associated with myocarditis or extracardiac factors, such as anemia Softening with prolongation or splitting of the first sound at the apex is a frequent early sign and may occur as a manifestation or prolongation in atrioventricular conduction or myocarditis, as well as early mitral valvulitis. The development of a blowing systolic murmur at the apex or a significant change in the quality of a pre-existent murmur is very common during acute rheumatic fever and may result not only from mitral valvulitis, but also from dilatation of the mitral ring in the absence of a lesion of the cusps The differentiation during the acute phase of the disease is often difficult. A systolic murmur produced by acute inflammation of the mitral leaflet tends to replace the first heart sound and to extend through most of systole, whereas a murmur produced by dilatation of the mitral ring tends to follow the first sound and terminate earlier. The former is characteristically harsh or musical and well transmitted to the axilla; the latter is typically soft, blowing and poorly transmitted. Often the final decision must be postponed until long after subsidence of all signs of rheumatic activity; murmurs due to organic mitral valvulitis should persist; those caused by relative mitral insufficiency should disappear.

The development of acute aortic valvulitis, severe enough to cause regurgitation, is easily recognized by the appearance of a cavernous blowing diastolic murmur in the third and fourth interspaces along the left sternal border. Murmurs referable to acute aortic or mitral valvulitis, which develop or undergo modifications during the course of acute rheumatic fever, may occur not only as a manifestation of acute rheumatic valvulitis, but also as a result of superimposed bacterial endocarditis. The latter is diagnosed in the presence of complicating systemic embolism and the etiologic agent is identified by blood culture.

Chronic (Inactive) Rheumatic Valvulitis is the end result of healing of the acute inflammatory lesions by fibroblastic ingrowth and gradual deposition of scar tissue.* Comparable deformities are prone to develop in the atrioventricular and aortic valves during the healing process. The regurgitation resulting from defective apposition of the acutely inflamed leaflets becomes permanently established as the healing causes retraction and eventually becomes complicated by stenosis as the scar tissue causes thickening, stiffening and fusion of the leaflets. Thus, the healing of rheumatic valvulitis tends to produce ultimately a combination of insufficiency and stenosis; however, all gradations are observed both clinically and pathologically from a simple insufficiency to a relatively pure stenosis. The lesion is most common in and often limited to the

* Inasmuch as the Aschoff body is the only accept-

mitral valve; aortic valvulitis is next most common; tricuspid valvulitis is much less frequent and is almost invariably accompanied by mitral stenosis. Lesions of the pulmonary valve are extremely rare. Clinicopathologic correlations will be made for each valve separately, multivalvular lesions tend to produce summation effects.

Chronic mitral valvulitis. Mild lesions may merely cause mitral insufficiency, severe lesions usually produce combined insufficiency and stenosis, but less commonly may cause relatively pure insufficiency or stenosis.

Mitral insufficiency. Mitral insufficiency is manifested by a systolic murmur, loudest at the apex and transmitted towards the axilla. Organic mitral insufficiency caused by rheumatic valvulitis is distinguished from relative mitral insufficiency resulting from left ventricular enlargement by the quality and duration of the murmur and particularly by its effect on the first heart sound. The murmur of rheumatic mitral insufficiency is characteristically harsh or musical and tends to replace the first heart sound and to continue through systole, whereas that of relative insufficiency is typically soft and blowing, tends to follow the first sound and to fade into mid-systole. A systolic thrill is occasionally palpable at the apex in rheumatic mitral insufficiency. The degree of organic mitral regurgitation cannot be judged from the quality, intensity or duration of the murmur but can be estimated from the size of the left ventricle and atrium, provided other causes of enlargement of these chambers are excluded. On this basis, rheumatic mitral insufficiency may be divided into two grades, mild and severe. In the former, there is little reflux of blood into the left atrium, absence of cardiac enlargement, and an asymptomatic course, provided bacterial endocarditis does not develop. In the latter, there is considerable regurgitation of blood, leading to compensatory dilatation and hypertrophy of both the left ventricle and left atrium, secondary pulmonary congestion and right ventricular dilatation and hypertrophy. In practically all the cases with clinical evidence of marked organic insufficiency, some degree of stenosis is demonstrable at autopsy; in many of these, careful auscultation during life will disclose a short protodiastolic rumbling apical murmur which is representative of the stenosis.

Mitral insufficiency and stenosis. Mitral insufficiency is manifested by the signs described above and the degree of regurgitation is estimated from the size of the left ventricle, provided other causes of enlargement are excluded. Mitral stenosis is manifested by a low-pitched rumbling diastolic murmur, maximal at the apex and often confined to a small area. The length of the murmur provides a rough index of the degree of stenosis. With milder degrees of stenosis, the murmur is usually confined to protodiastole, occasionally to presystole, with moderate degrees it is heard in both of these phases, but fades in mid-diastole, with severe degrees it extends throughout diastole. The more pronounced murmurs are accompanied by a diastolic thrill.

Both mitral insufficiency and stenosis cause gradually increasing elevation of pressure in the left atrium, thence in the pulmonary veins, capillaries, arteries and trunk and right ventricle. The rising pressure is accompanied by gradual enlargement of the left atrium, slowly increasing passive congestion of the lungs, dilatation of the pulmonary vascular tree and compensatory dilatation and hypertrophy of the right ventricle.

As the left atrium dilates, it extends backward and to the right. The enlargement of the left atrium is detectable roentgenologically, both by direct visualization

in the oblique position and by compression and displacement of the esophagus. The latter is occasionally sufficiently marked to produce dysphagia. In long-standing cases, the left atrium may reach enormous size and may form the right boundary of the heart.

Dilatation of the pulmonary trunk is manifested by the following signs in the second interspace at the left sternal border. an abnormally prominent systolic pulsation, a diastolic shock, a blowing systolic murmur and an abnormally accentuated pulmonic second sound Severe and long-standing dilatation of the pulmonary trunk may be accompanied by relative pulmonary insufficiency, manifested by a cavernous blowing diastolic murmur, following the second sound in the second and third interspaces at the left sternal border, louder in the recumbent than in the erect position This is known as the Graham Steell murmur and resembles that of aortic insufficiency in quality, but differs in location and in postural influence, however, it can be diagnosed only in the presence of marked dilatation of the pulmonary trunk together with absence of peripheral signs of aortic insufficiency.

The gradually increasing pulmonary congestion is manifested by slowly increasing exertional dyspnea for a long but variable period of time Compensation is maintained through right ventricular dilatation and hypertrophy, the signs of which have been described on pages 921 and 922. Under stress of the progressively increasing pulmonary vascular pressure, engorged vessels may rupture, causing repeated gross hemoptysis.

Right ventricular failure is prone to occur eventually and is usually gradual in development. Sudden failure may be precipitated by the advent of atrial fibrillation, pulmonary embolism, bronchopulmonary infection, or by acute myocarditis associated with recurrent rheumatic fever. Decompensation associated with mitral valvulitis usually responds well to bed rest, together with the customary medical measures, so that most patients have had a number of bouts of failure prior to the fatal episode.

Mitral stenosis. In a number of cases, the clinical signs are representative of a relatively pure mitral stenosis, namely, a normal-sized left ventricle, a slapping rather than a heaving apical impulse, a snapping apical first sound with little or no systolic murmur, but with a typical diastolic rumble. The latter usually extends throughout diastole, indicating a marked degree of stenosis. Dilatation and hypertrophy of the left atrium, engorgement of the pulmonary vessels, passive congestion of the lungs and right ventricular dilatation and hypertrophy occur, as in combined mitral insufficiency and stenosis. The foregoing findings can be correlated with the fish-mouth type of mitral orifice, exhibiting pathologically a marked degree of stenosis and a relatively slight insufficiency.

Aortic valvulitis. At the advent of acute rheumatic aortic valvulitis, a cavernous blowing diastolic murmur, best heard in the third and fourth interspaces along the left sternal border, may constitute the only clinical sign. As healing occurs, this murmur persists and tends to lengthen in duration, to increase in intensity and to be transmitted to the left axilla. Although audible in the second interspace at the right sternal border, the diastolic murmur of rheumatic aortic insufficiency is loudest along the left sternal border.

Peripheral signs of aortic regurgitation may appear and are proportionate to the degree of regurgitation. The earliest evidence is an increase in pulse pressure which results primarily from lowering of diastolic pressure, secondarily from elevation of systolic pressure. Water-hammer pulsations, characterized by sudden im-

pact and precipitous collapse, become visible and palpable in the peripheral arteries. The elevation in systolic pressure is disproportionately great in the femoral, as contrasted with the brachial artery, and the abruptness of the systolic distention of the femoral artery gives rise to a pistol-shot sound over the vessel. Other peripheral signs that may be elicited, not only in aortic insufficiency, but also in other conditions accompanied by high pulse pressure and peripheral arteriolar dilatation, include Duroziez's sign, a to-and-fro murmur, heard upon application of pressure to a stethoscope over the femoral artery, and Quincke's capillary pulse, an alternate blanching and flushing of the nail bed, brought out during pressure against the tip of the nail.

A systolic aortic murmur, if not present during the acute stage, becomes audible in the second interspace at the right sternal border and is transmitted into the neck vessels. As the valvular cusps thicken and stiffen, this murmur becomes louder, harsher, more prolonged and widely transmitted over the whole precordium. In the event of death at this stage, some degree of stenosis, as well as insufficiency, is generally demonstrable at autopsy, however, a clinical diagnosis of aortic stenosis is reserved for cases in which the murmur is accompanied by a palpable systolic thrill in the second interspace at the right sternal border, or by disappearance or marked diminution of the aortic second sound, or by typical peripheral signs, namely, a small plateau pulse and low pulse pressure In long-standing cases of rheumatic aortic valvulitis, stenosis may be the major or the only clinically demonstrable defect; however, some degree of associated incompetence is found at autopsy. During decompensation, the thrill of aortic stenosis disappears and the murmur tends to become muffled and softened, hence the diagnosis may be missed if the patient is not re-examined after compensation is restored or if he dies during failure.

In chronic aortic valvulitis, a systolic and usually a diastolic murmur are audible at the apex. These murmurs are referable to an associated mitral valvulitis in the majority of cases, but may be produced at the mitral orifice in the absence of an intrinsic lesion A systolic murmur, loudest at the apex and transmitted to the axilla, may be found as a result of relative mitral insufficiency secondary to left ventricular enlargement. A rumbling apical diastolic murmur and even an associated diastolic thrill, indistinguishable from that of mitral stenosis, may be found in isolated aortic insufficiency. This is known as the Austin Flint murmur and is prone to occur in association with incompetence of the posterior aortic cusp Under these circumstances, the regurgitant stream is directed against the anterior leaflet of the mitral valve and tends to force it closed, thereby producing the diastolic murmur.

Both aortic insufficiency and stenosis tend to produce progressive left ventricular hypertrophy and dilatation, signs of which have been described on pages 919 and 920 Despite the chronically increased load on the left ventricle, compensation is often maintained for years Failure is often ushered in abruptly either by violent exercise or as a paroxysm of nocturnal dyspnea Even though the patient survives the initial attack of acute left ventricular failure, the therapeutic response is generally poor and at first chronic left, then right ventricular failure supervenes.

Angina pectoris is present in a small percentage of cases of rheumatic aortic valvulitis, particularly when stenosis is the predominant lesion. The clinical coronary insufficiency may be correlated with independent coronary atherosclerosis in some cases, but occurs in the presence of relatively normal coronary arteries in others.

In the latter, proper coronary filling may be hindered during systole by excessively high intraventricular pressure in aortic stenosis and may not occur during diastole in aortic insufficiency, as a result of the low diastolic pressure and regurgitation of blood, ordinarily available for coronary filling, into the left ventricle.

Syncope is not uncommon in aortic stenosis and is an expression of cerebral ischemia, usually because of inability of the left ventricle suddenly to augment its output, but is sometimes referable to a hyperactive carotid sinus reflex. Complete atrioventricular block and left bundle branch block may complicate rheumatic aortic valvulitis and may sometimes be correlated with extension of calcification from the base of the cusps into the membranous portion of the septum

Tricuspid valvulitis is rarely an isolated lesion, but is almost invariably accompanied by mitral stenosis and insufficiency. The clinical manifestations referable to the mitral valvulitis appear first and those of tricuspid insufficiency become superimposed much later. Dyspnea decreases in severity, owing to shift of blood from pulmonary to systemic circulation, exceptions to this generalization being traceable to pleural effusion or massive ascites. On the other hand, cyanosis increases because of peripheral capillary stasis, and is frequently mixed with icterus, secondary to hepatic engorgement, to make a greenish hue. Abdominal swelling from ascites is usually a prominent symptom and is generally disproportionate to edema. In this respect, tricuspid regurgitation bears resemblance to constrictive pericarditis, the distinction is readily made in these cases by the venous pulsatile phenomena and right ventricular dilatation and hypertrophy characteristic of tricuspid regurgitation.

Elevation of venous pressure is evidenced by dilatation of the cervical veins in the erect position The distinctive feature, however, is a systolic venous pulsation caused by regurgitation of blood through the tricuspid orifice into the venae cavae, rather than the usual systolic collapse from atrial filling. The systolic pulse is well seen in the external jugular vein and is made out in the internal jugular vein by lifting of the sternomastoid muscle.

The discharge of blood from the right ventricle into the hepatic vein produces systolic swelling of the markedly enlarged liver, manifested by systolic protrusion of the right costal margin and a systolic expansion and descent of the liver edge The rapid escape of large amounts of blood from the right ventricle into the liver not only causes protrusion of the lower right chest, but tends to produce systolic retraction of the apex as a result of sudden reduction in intrathoracic pressure. Added to these pulsatile phenomena is systolic protrusion of the sternum caused by the associated right ventricular hypertrophy and dilatation. Although the foregoing signs may be observed during failure, as a result of relative tricuspid insufficiency as well as tricuspid valvulitis, they tend to clear up rapidly with therapeutic response in the former situation, but persist in the latter.

Auscultatory phenomena are of little significance in the diagnosis of tricuspid disease inasmuch as murmurs derived from the associated mitral valvulitis are often audible in the tricuspid area and are similar in quality to tricuspid murmurs. Tricuspid regurgitation tends to produce a systolic murmur, loudest at the xiphosternal junction. The association of tricuspid stenosis with mitral stenosis is postulated when there are two rumbling diastolic murmurs, one localized at the tricuspid area, the other at the apex. The combination of tricuspid stenosis and insufficiency may result in double pulsation in the cer-

vical veins, the first impulse being caused by contraction of the hypertrophied right atrium, the second by systolic discharge of blood from the right ventricle into the superior vena cava.

SYPHILITIC AORTIC INSUFFICIENCY

The principal cardiac lesions caused by syphilis, namely, aortic insufficiency and narrowing of the coronary ostia, represent complications of the dilatation and scarring of the root of the aorta, produced by the specific aortitis. Dilatation of the root of the aorta from syphilis tends to produce pure aortic incompetence, both by separation of the cusps at their commissures and by rolling of the free margins of the cusps.

Clinical Differentiation of Syphilitic from Rheumatic Aortic Insufficiency is based chiefly on (1) evidence of dilatation of the aorta in the former and a normal-sized aorta in the latter, and (2) signs of pure aortic regurgitation in the former, as contrasted with varying degrees of associated stenosis in the latter The dilatation of the ascending aorta that constitutes a forerunner of syphilitic aortic insufficiency is first detectable roentgenologically and later is manifested by significant physical signs in the second interspace beyond the right sternal border, namely, an abnormal pulsation, percussion dullness, a soft blowing systolic murmur, and an accentuated tambour aortic second sound. Fusiform dilatation or saccular aneurysm of the arch or descending aorta may also be present and aids in establishing the syphilitic etiology of the lesion clinically.

Significant differences in the character and distribution of murmurs associated with syphilitic and rheumatic lesions of the aortic valve can often be made out clinically and can be correlated with differences in underlying pathology. The systolic component of the murmur in syphilitic aortic insufficiency is short and soft and represents vibration of the aortic walls, produced by eddy currents set up in the dilated aorta, the systolic component in a healed rheumatic lesion is long and harsh and is eventually accompanied by a palpable thrill, representing coarse vibrations in the stiffened cusps projecting into the outflowing stream. On the other hand, the diastolic component of the murmur is generally longer and more intense in the syphilitic lesion, reflecting the greater degree of regurgitation. Furthermore, the diastolic murmur in syphilitic aortic insufficiency is well heard along the right sternal border and is often maximal in this area, as the result of the dilatation of the aorta to the right, whereas the corresponding murmur in rheumatic aortic insufficiency is poorly heard to the right of the sternum and is almost invariably maximal along the left sternal border.

Although mitral valvular lesions are not produced by syphilis but are generally present in patients with rheumatic aortic insufficiency, auscultatory findings at the apex are of little help in clinical differentiation, because of the fact that syphilitic aortic insufficiency produces left ventricular enlargement and relative mitral insufficiency and at the same time may be accompanied by a rumbling diastolic (Austin-Flint) murmur at the apex, simulating that of mitral stenosis The Austin-Flint murmur is prone to occur when the posterior cusp is incompetent, permitting the regurgitant stream to strike and partially close the anterior mitral leaflet The rumbling apical diastolic murmur thereby produced may simulate that of organic mitral stenosis in quality, may equal or exceed it in intensity and, indeed, may be accompanied by a diastolic thrill.

The peripheral signs of syphilitic aortic insufficiency are similar to those of rheumatic aortic insufficiency described on page 940, but are usually more pro-

nounced, owing to the greater degree of regurgitation usually associated with syphilitic than with rheumatic lesions and the absence of a stenotic component in the former.

Progressive left ventricular dilatation and hypertrophy are produced by syphilitic aortic insufficiency but compensation is often maintained for years after appearance of the valvular defect. Break in compensation is often sudden, taking the form of a severe paroxysm of nocturnal dyspnea or acute left ventricular failure during violent exertion. Even though compensation is restored, adequate exercise tolerance is seldom regained Left ventricular failure tends to recur soon and is likely to be followed by right ventricular failure.

Myocardial ischemia from narrowing of the coronary ostia is a contributory factor towards the failure in some cases A clinical diagnosis of myocardial ischemia is permissible, however, only in the presence of angina pectoris or electrocardiographic signs of transitory subendocardial injury (page 934) Under these circumstances, narrowing of the coronary ostia is generally demonstrable at autopsy

BACTERIAL ENDOCARDITIS

The subacute form is superimposed upon valves damaged as a result of previous inflammation or congenital defects and is caused by *Streptococcus viridans* or other organisms of relatively low virulence, the acute form may develop on previously normal valves and is caused by pyogenic organisms of high virulence, such as the Pneumococcus; however, correlation between clinical and pathologic findings follows similar patterns in the two forms of the disease. The main features are classifiable into three groups: (1) constitutional signs; (2) cardiac signs; and (3) embolic and vascular lesions.

Constitutional Signs. Fever is the commonest manifestation, but may be absent in terminal or very low-grade infections. It is typically of the picket-fence type with chills and sweats but may be continuous or remittent. Leukocytosis is usual but not invariable. Progressive anemia develops and may be accompanied by tenderness over the sternum or other bones. Clubbing of the fingers is generally demonstrable in the subacute form of the disease.

Cardiac Signs. When subacute bacterial endocarditis is engrafted on rheumatic valvulitis, it is not uncommon to find, in addition to the old rheumatic lesions, both clinical and pathologic evidence of recent reactivation of the rheumatic valvulitis. Changes in quality or intensity of preexistent murmurs are prone to occur in subacute bacterial endocarditis but are not diagnostic, since they are also observed as a result of acute rheumatic valvulitis and extracardiac factors. Acute bacterial endocarditis during the course of a pyogenic infection may be manifested by the abrupt appearance of a loud, rough murmur, generally systolic with mitral involvement, diastolic with aortic. Clinical and electrocardiographic evidence of complicating myocarditis (pages 945 and 946) is fairly common. The severe grades can be correlated with diffuse inflammatory lesions at autopsy. Myocardial infarction may result from coronary embolism.

Embolic and Vascular Manifestations. A wide variety of clinical and pathologic manifestations result from fragmentation of the vegetations and dispersal through the blood stream of emboli ranging in size from particles capable of obstructing major arteries to particles which lodge in arterioles or capillaries. The systemic circuit receives the emboli in most cases, since the vegetations are generally located on the mitral and/or aortic valves; pulmonary embolism complicates vegetative endocarditis of the right side of the heart.

Large emboli, reaching the extremities,

may produce typical clinical and pathologic signs of arterial occlusion. Much more frequent and, therefore, of greater diagnostic value are the clinical signs of arteriolar and capillary lesions in the skin and mucous membranes, presumably produced by minute emboli. These consist of white-centered petechial hemorrhages, best made out in the conjunctiva, tender, bluish red nodules in the pads of the fingers and toes (Osler nodes), and splinter hemorrhages in the nail beds.

Large emboli to the abdominal viscera give rise to sudden pain of a type and distribution characteristic of irritation of the peritoneal surface or capsule of the involved organ Thus, a renal embolus of sufficient size to produce an infarct is manifested by sharp pain in the loin, which may radiate forward and downward to the groin and is accompanied by hematuria. A more common renal manifestation is painless microscopic hematuria without renal insufficiency, which may be correlated with focal embolic glomerulitis Acute diffuse glomerulonephritis with edema, hypertension and renal insufficiency, in addition to the hematuria and albuminuria, is also encountered, particularly late in the disease, when the blood culture is sterile The spleen is generally enlarged sufficiently to be detectable by palpation

Cerebral embolism produces neurologic findings, which can be correlated accurately with the site of the lesion. Meningeal irritation with increased number of leukocytes or red cells in the spinal fluid is not uncommon, even in the absence of focal cerebral signs

Myocarditis

There is often a lack of correlation between pathologic evidence of myocarditis encountered at autopsy and clinical and electrocardiographic manifestations found during life The discrepancy arises in part from the fact that focal patches of acute myocarditis are demonstrable at autopsy in a number of patients in whom no cardiac lesion had been suspected during life. Some of these cases have escaped clinical detection, despite daily observation by a competent cardiologist and frequent serial electrocardiograms employing multiple precordial leads The discrepancy is also explained in part by the fact that some patients with fatal infections have had physical or electrocardiographic changes attributed to acute myocarditis during life, but have shown no significant pathologic changes in the heart at autopsy Nonspecific cardiac signs, which may develop during the course of severe infection, not only as the result of acute myocarditis, but also as a manifestation of extraneous factors, such as anemia, peripheral circulatory collapse, and hypopotassemia, include the following: tachycardia disproportionate to fever; softening of the first sound at the apex, even to the point of tic-tac rhythm, a blowing systolic murmur at the apex, or a mesodiastolic gallop rhythm, occurring at rates above 120. Nonspecific electrocardiographic abnormalities developing during the course of infection, which may be produced not only by myocarditis, but also by various metabolic abnormalities, particularly hypopotassemia, include RS-T depression, flattening or inversion of the T waves, lengthening of the Q-T interval, and prolongation of the P-R interval.

Correlation between clinical and pathologic findings is closer in patients with infections who develop myocarditis severe enough to cause death Demonstrable cardiac enlargement developing during the course of infection points strongly to acute myocarditis. The appearance of a protodiastolic gallop rhythm at rates below 100 in patients with severe acute infections also constitutes presumptive evidence of acute myocarditis. The development of

congestive failure during the course of infection in a patient with a previously normal heart, who has not received excessive doses of saline parenterally, constitutes a basis for a diagnosis of acute myocarditis. Shock (characterized by ashen-gray cyanosis, rapid, thready pulse, and cold, clammy extremities) may occur during the course of acute infection, as a result of severe myocarditis, or as a result of peripheral circulatory collapse. In the former, the neck veins may be distended, whereas in the latter they are collapsed.

The following electrocardiographic abnormalities, developing during the course of an acute infection, can be correlated with acute myocarditis: complete A-V block, high-grade partial A-V block, low-grade A-V block not abolished by atropine, bundle branch block, and intraventricular conduction defects. Atrial fibrillation or flutter may occur as a manifestation of atrial myocarditis.

When the inflammatory process reaches the endocardium, mural thrombi may be formed in one or more chambers and may be dislodged to act as emboli in the systemic and/or pulmonary circuit. The inflammatory process may also extend into the pericardium to give rise to typical signs of acute pericarditis (page 936).

Chronic infectious granulomas of tuberculosis and the mycoses, and sarcoidosis may occasionally develop in the myocardium but are usually undetected clinically unless numerous or large, or unless they undergo suppuration and break into the pericardium or through the endocardium.

The patchy acute myocarditis which occurs in some cases of trichinosis may be asymptomatic or may be accompanied by physical and electrocardiographic signs listed above as nonspecific. Congestive failure is very rare. In echinococcosis cysts are found in the heart in about one per cent of those infected. Calcified cysts have been demonstrated roentgenographically.

TRAUMA

Penetrating Lesions. Hemopericardium constitutes the *predominant* feature in those surviving the first few minutes. Rapid accumulation of blood produces cardiac tamponade, manifested by a rising venous pressure, falling pulse pressure, feeble paradoxic pulse, and a quiet heart with muffled sounds and small excursions on fluoroscopy. The *roentgen silhouette* need not be grossly enlarged at the time the foregoing triad is present. The electrocardiogram may be negative when clinical manifestations of hemopericardium first become evident but sooner or later shows changes typical of pericarditis, namely, elevated, upwardly concave RS-T segments in leads from opposite surfaces of the heart, associated with a reduction in QRS voltage, but no abnormality in QRS contour. These RS-T patterns show the characteristic evolution of pericarditis, the junctions progressively approaching the isoelectric line and the T waves meanwhile undergoing progressive cove-plane inversion. When the injury has caused extensive myocardial contusion or when a coronary artery has been severed or ligated at operation, abnormal Q waves typical of those found in myocardial infarction are demonstrable. Valvular rupture in the course of the penetrating wound is manifested by a loud, coarse sea-gull type of murmur and is generally complicated by acute congestive failure.

Non-penetrating Injuries. Crushing injuries and direct blows to precordium from objects traveling at high *velocity* have caused cardiac rupture with hemopericar-

dium, myocardial contusion, and rupture of a valve or *chordae tendineae, even in* the absence of fracture of the thoracic cage. Cardiac rupture from non-penetrating injuries causes tamponade similar to that resulting from penetrating wounds. Gross myocardial contusion without rupture may be accompanied by symptoms, signs and electrocardiographic changes *simulating those of acute myocardial in*farction and may heal to leave a cardiac aneurysm. Death during the acute stage may result from ventricular fibrillation or standstill. Atrial injuries by indirect blows may be complicated by atrial fibrillation or flutter, *generally transitory* Rupture of the aortic valve by non-penetrating injuries is manifested by the sudden appearance of a loud sea-gull diastolic murmur over the whole precordium, accompanied by peripheral signs of aortic regurgitation and by rapid development of congestive failure. Rupture of the mitral valve or chordae tendineae caused a loud, coarse systolic murmur and thrill, maximal at the apex and transmitted over the whole precordium, and is generally followed by congestive failure

NEOPLASMS

The majority of cardiac neoplasms found at autopsy produced no clinical manifestations during life In some patients dying of malignancy with asymptomatic cardiac metastases, thorough cardiac examination has revealed nonspecific electrocardiographic abnormalities and occasionally diagnostic roentgen signs, namely, nodular irregularity in the cardiac silhouette.

Striking clinical features referable to the heart are *present in a few* cases of primary and metastatic neoplasm and are classifiable into the following syndromes

Chronic cardiac tamponade may occur from neoplastic invasion of or effusion into the pericardium A suspicion of neoplastic etiology is engendered by hemorrhagic character of the fluid, by rapid recurrence after tapping and may be confirmed roentgenologically in some cases by demonstration of nodules after instillation of air. A positive diagnosis has been established in some cases by demonstration of neoplastic cells in the aspirated pericardial fluid.

Superior vena caval obstruction without demonstrable bronchogenic or mediastinal *neoplasm or aneurysm should suggest* neoplasm of the right atrium

Intractable congestive failure may be produced by extensive neoplastic invasion of the myocardium An antemortem diagnosis may be possible through elimination of other causes of congestive failure and demonstration of irregularities of roentgen silhouette consistent with neoplasm. Clinical signs of mitral stenosis have been produced by myxoma of the left atrium and *acute attacks of pulmonary edema* have occurred from obstruction of the mitral orifice by a pedunculated tumor and have been relieved by changes in posture.

The development of atrioventricular block in persons with known malignant neoplasms may indicate metastasis to the nodal tissues and the occurrence of unexplained atrial fibrillation should arouse the suspicion of atrial involvement by neoplasm.

A diagnosis of rhabdomyoma can be established clinically by the association of abnormalities in cardiac roentgen silhouette *with mental retardation, tuberous scle*rosis and adenoma sebaceum.

Gross Examination of the Heart
Injection of Coronary Arteries
Weights and Measurements of Heart

OTTO SAPHIR

*Non vi sed arte.**

GROSS EXAMINATION OF THE HEART

THE GROSS examination of the heart is only a part of the complete autopsy, and subsequent histologic examination must be carried out in the elucidation of the morphologic changes produced by disease and their influence in the causation of death. While it is essential to make a careful examination of the exterior of the body, the serous cavities, all the organs and the peripheral vascular bed, only the technic of opening and dissecting the heart will be considered here. Of the several methods, only one will be described in detail and two others will be mentioned briefly. Extensive experience points to the importance of opening the heart in conjunction with the lungs and great blood vessels. Thus, the aorta must be opened in continuity with the aortic valve and left ventricle, and the pulmonary trunk in continuity with the right ventricle, pulmonary valve and lungs. Although such a dissection in conjunction with adjacent structures may be cumbersome, a number of details are likely to be missed if the heart is separated from the rest of the organs and examined alone.

The following *instruments* are recommended for dissection of the heart: a knife with a long-bladed single cutting-edge, often called an amputation knife; an enterotome; a small dissecting scissors, to open the branches of the coronary arteries, one or two pairs of forceps, several hemostats and a probe.

If a *blood culture* is desired the sample of blood should be removed from the

* "Not by force, but by art." From *Iliad*, Book 23

heart at the beginning of the autopsy. The pericardial sac is incised and the ventral surface of the right atrium cauterized with a hot spatula. The blood for culture of organisms is drawn from the right atrium with a sterile needle and syringe or with a pipet. Gentle pressure upon the liver will aid in obtaining the sample.

In the following discussion it is assumed that the autopsy has progressed to the stage where it is possible to remove the heart, large vessels, lungs and the ascending aorta *en masse*, after cutting the descending aorta just above the diaphragm These organs are placed on the autopsy table with the ventral surfaces of the lungs and heart in the immediate view of the prosector, the arch of the aorta being directed away from him As stated above, the heart during its dissection must be left in continuity with the surounding structures. The pericardial sac is now opened by means of scissors, if it has not previously been opened in order to take a specimen of blood for culture It is incised in the region of the apex of the heart and a triangular flap is cut in the ventral portion of the parietal pericardium, the flap corresponding roughly to the size of the ventral wall of the heart This flap is reflected cephalically from the heart but left attached to the aorta in the region of the reduplication of the pericardium. Care must be taken to observe the type and amount of fluid which is present within the pericardial cavity.

Before opening the heart it is sometimes imperative to ascertain the presence of *air* or *fat emboli* in the right ventricle or pulmonary trunk To demonstrate air emboli, water is introduced into the pericardial sac, the incised sac being held taut with hemostats or forceps applied to its cut edges. The right atrium may now be opened under water and the escape of air bubbles observed. Minute air bubbles, indicating postmortem decomposition, are almost constantly noted If facilities are available it is better to immerse both the heart and the lungs in a deep pail of water. Thus, the pulmonary trunk can be opened under water, slight pressure exerted upon the right ventricle causing the escape of air from the right ventricle. Fat emboli might also be demonstrated.

Air Embolism. A practical device for demonstrating air embolism was recommended by Kulka (1949). This method can be used for quantitative and qualitative demonstration of air or other gases that may be present in the cardiac ventricles Figure XIV-1 shows the apparatus for the demonstration of air embolism. The apparatus consists of the following parts.

A. A wide-mouthed glass bottle of 2- or 3-ounce (60 to 90 ml) capacity, fitted tightly with a two-holed rubber stopper.

B. Two sections of glass tubing with an inside diameter of approximately 3 mm, each section being bent at an angle of 120 degrees. One of these sections should be longer than the other The shorter one should reach just through the stopper and be even with the inner surface of the stopper The longer one should reach to within 1 or 1 5 cm of the bottom of the flask. Both tubes should fit tightly into the holes of the stopper

C. One separatory funnel (pear-shaped and of 60- to 100 ml. capacity) connected to the longer section of bent glass-tubing by rubber tubing 100 cm. in length (F). An amber, pure-gum rubber tubing such as is used on blood diluting pipets has proved satisfactory.

D. One transfusion needle, No. 14 or 15 gauge, 4 or 5 cm. in length, connected to the shorter glass tube by a short section of rubber tubing not exceeding 5 cm. in length (F).

E. Two pinchcock clamps, one for each length of tubing. They may be of the spring type or of the household-syringe type. The latter will prove advantageous

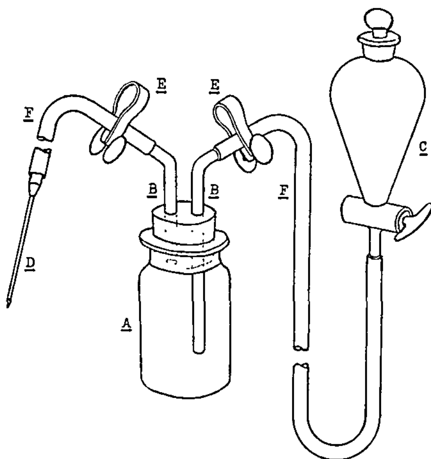


Figure XIV-1 A device by Kulka for demonstrating air embolism (See text for the explanation of this diagram) (Taken from Kulka, W . A practical device for demonstrating air embolism *Arch Path*, *48* 366-369, 1949. Courtesy of *Archives of Pathology*)

if the gas collected is to be transported for analysis.

The entire system is filled with liquid petrolatum so that when the funnel is at a level with the upright bottle the oil fills about one-half of the funnel.

Technic. In operation the funnel is first raised to a position 30 or 40 cm. above the level of the upright bottle. All the cocks are opened and the position is retained until every trace of gas has been driven from the system through the needle which is thereby coated on the inside by a film of oil. After all air has been expelled, the cocks are closed and the funnel lowered once again to its original position.

As a precautionary measure and control, the airtightness of the whole system should be tested before operation. This is done by inserting the needle into musculature or skin and attempting to induce aspiration in the following manner: The bottle is inverted and the needle inserted into the cavity in question. When the needle is in position, all cocks are opened The funnel is lowered about 70 to 90 cm, or until adequate suction is created. The contents of the cavity are thereby aspirated. The contents may be air or other gases, either pure or mixed with blood or other liquid. Any gas or liquid entering this system may be observed through the wall of the short bent glass-tubing If the test is positive, gas bubbles will collect in the bottle above the level of the oil. If desired, this gas may now be saved for further examination by closing all the cocks and returning the bottle to its upright position.

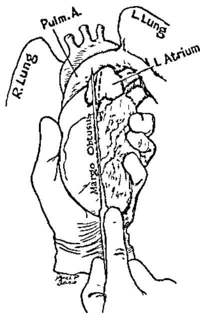


Figure XIV-2 Diagram showing *method of first incision, along the* left lateral margin of the left ventricle (Figures XIV-2 to XIV-10 reproduced, courtesy of Paul Hoeber Co)

Opening the Heart. *The heart is now* lifted up from the posterior parietal pericardium, and held with the left hand in such a fashion that, if normal in size, it is almost completely encircled, the four fingers and the palm encircling the right ventricle, the thumb partially encircling the left ventricle. The heart is rotated about 90 degrees so that its left margin (margo obtusus), exposed between the thumb and the tips of the fingers, faces the prosector. The long knife held in the right hand now cuts the left ventricle along its left lateral margin (Figure XIV-2) The four fingers of the left hand are now inserted into the left ventricular cavity through this cut and the ventral wall of the left ventricle is held between the thumb and the four fingers. The apex is raised from the table and the heart tilted so that the line of the margo obtusus forms an angle of about 90 degrees with the aorta A large knife (amputation knife) is held near the end of the handle and loosely between the thumb, index and middle fingers of the right hand, and made to pierce the apical portion of the wall of the *right ventricle* at its lateral margin (margo acutus) and penetrate the right ventricle. It is directed through the right ventricular cavity and through the tricuspid orifice and pierces *the right lateral* wall of the right atrium from within, the tip of the knife emerging through its lateral margin (Figure XIV-3). These openings in the right ventricle and *right atrium* are connected by splitting open the right ventricle along its lateral margin (margo acutus), with the blade of the knife resting in the right ventricle. This incision is made from within the ventricle and atrium It *exposes the right ventricular cavity and a* portion of the right atrium and cuts through the *tricuspid valve* along its right lateral margin. The heart is now again placed in its normal position and the blunt blade of an enterotome is introduced into the right atrium which is completely opened by continuation of the ventricular incision. From the atrium the enterotome is also inserted into the superior and in-

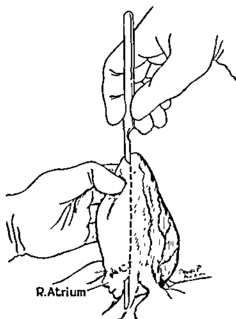
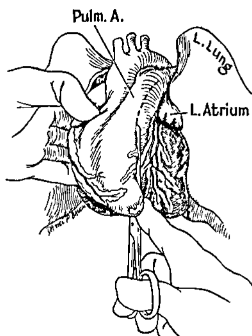


Figure XIV-3 Diagram showing the path of the incision along the lateral margin of the right ventricle The blade cuts from within the ventricle and atrium



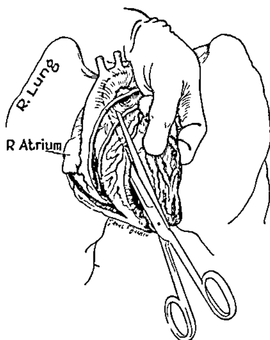


Figure XIV-4 Diagram of incision through the wall of the right ventricle.

Figure XIV-5 Incision of the ventral wall of the left ventricle. The flap cut from the wall is retracted with the left hand while with the right hand the blade is introduced into the ventricle

ferior *venae cavae*, both of which are now opened by continuing the atrial incision The presence or absence of an open *foramen ovale* may be ascertained now.

The pulmonary valve and the *pulmonary trunk* are exposed next. The heart is maintained in its normal position. The four fingers of the left hand are placed into the right ventricular cavity and the ventral wall of the right ventricle is held between them and the thumb. With the enterotome directed by the right hand, an incision is made through the wall of the right ventricle, producing a roughly triangular flap (Figure XIV-4). This incision starts at the apex, extends very close and parallel to the interventricular septum and cuts through the pulmonary valve and the pulmonary trunk. After completion of this incision the opened pulmonary trunk is immediately examined for the presence of an embolus. For this purpose the vessel is carefully washed with a stream of water. If there is a patent *ductus arteriosus* it may also be noted now. The right chambers and the tricuspid and pulmonary valves are now examined. It is imperative to look for mural thrombi in the right *auricular appendage*. In this examination it is recommended that a small portion of the sharp edge of the appendage be cut with the scissors from the outside, and the inner wall examined through this incision.

Completion of the opening of the left side of the heart follows. The left ventricle was previously opened along its lateral margin. The index finger of the right hand is now introduced into the *left atrium* through the mitral valve to palpate for evidence of stenosis of its orifice. If the orifice is stenotic a different procedure is indicated which will be referred to later. If stenosis is not manifest the blunt blade of the enterotome is introduced through the *mitral valve* into the left atrium and both the valve and the atrium are cut open along the left lateral border of the heart by continuing the line of the first incision made to open the left ventricle. Care must be taken, in making this incision,

that the end of the enterotome is directed through the mitral orifice and not through the aortic orifice After the left atrium is exposed the *pulmonary* veins which enter into it should be opened and inspected. The presence or absence of a *foramen* ovale has been previously ascertained

The next and most difficult incision exposes the *aortic valve* and the ascending aorta. The heart is placed in its normal position. It is wise first to insert the index finger of the right hand through the aortic valve to determine if its orifice is stenotic. If stenosis is found a different procedure is indicated. This will be mentioned later *If there is no stenosis, the four fingers* of the left hand are placed in the cavity of the left ventricle. The ventral wall of the left ventricle is held between them and the thumb which should be in contact with the ventral surface of the left ventricle (Figure XIV-5) This position appears somewhat awkward since during the next incision the left hand, holding the flap cut from the ventral wall of the left ventricle, is placed above and across the right hand The blunt blade of the enterotome, held in the right hand, is introduced into the left ventricle and the ventral wall of the left ventricle is incised, the incision extending cephalically from the apex, parallel to and close to the septum through the aortic valve and into the ascending aorta This incision of necessity cuts through the pulmonary trunk which is transected above the pulmonary valve, care being taken that this valve is not injured. Such injury is avoided if the line of incision is directed just between the left auricular appendage and the outer aspect of the pulmonary valve which can easily be palpated. The aorta is opened to its arch and from there along its dorsal surface If the thoracic portion of the aorta, removed in continuity with the heart, has been previously opened, the enterotome, after opening the arch, is directed toward the line along which the descending thoracic aorta has been opened The left ventricle and particularly the mitral and aortic valves are carefully washed with a stream of water and may now be studied. During this procedure *care must be taken not to remove thrombi* which may be mistaken for clots. The latter are often yellowish and elastic and are easily removed by a stream of water. Thrombi, however, are grayish or dark red, attached to the wall and are not easily removable They may be ragged or smooth Often clots are heavily intermingled with vegetations of acute bacterial endocarditis or endocarditis lenta For distinguishing these, see page 711 The left auricular appendage must be examined for thrombi in a manner similar to that described for the right auricular appendage.

Procedure to be Followed in Stenosis of Valvular Orifices. Stenosis of the valvular orifices is best demonstrated in unopened valves Therefore, in instances of *stenosis of the mitral valve* a separate incision into the left atrium up to the mitral ring should be made, instead of continuing the ventricular incision through the mitral valve. This opening into the left atrium is made along the left lateral margin of the atrium following the line of the incision made to open the left ventricle. The exposure of the left atrium should be enlarged by opening the mouths of the pulmonary veins. Thus, the mitral orifice can easily be viewed. In instances of *stenosis of the aortic orifice* the incision which goes along the septum of the left ventricle must not be continued through the aortic valve, but terminated where the base of the aortic valve comes into view The ascending aorta is now opened, the incision starting at the termination of the incision which had been made to open the abdominal aorta; or an incision may be made into the aorta starting proximal to the opening of the *innominate artery. The line of the in-*



Figure XIV-6. Incision of the right atrium of an isolated heart. The incision is made between the openings of the inferior and superior venae cavae.

cision must correspond to the one made to open the left ventricle to expose the aortic valve The incision in the aorta extends up to the region of the sinus of Valsalva but does not pass through the aortic orifice. Thus a good view is obtained of the stenotic aortic valve, the sinus of Valsalva being readily visible from the aorta and the ventricular surfaces of the aortic cusps being visible through the ventricle.

Dissection of Isolated Heart. If on rare occasions the heart must be removed from the body and examined separately, the following technic may be used: The heart is grasped at the apex and pulled cephalically and ventrally, severing in succession, first the inferior vena cava, then the left pulmonary veins, the left pulmonary artery, the right pulmonary artery, the right pulmonary veins, the ascending aorta and finally the superior vena cava. These structures should be cut as far from the heart as possible so as not to injure the atria.

The heart is now opened and dissected only with the enterotome. It is opened the direction of the flow of blood. In general, as Farber (1937) stated, when scissors enter the ventricle the apex of heart is pointed away from the operat when the scissors leave the ventricle, apex of the heart is directed towards operator. The heart is held with the hand. On opening the atria the left ha encircles both ventricles. The enterotom introduced first through the inferior ve cava and extends into the opening of superior vena cava, and the right atri is cut between the openings of these t veins (Figure XIV-6). In opening right ventricle the heart again is held w the left hand, the lateral margin of right ventricle (margo acutus) facing prosector, and the atria being directed ward him. The enterotome is introduc into the right atrium, through the tricusp orifice, and the right ventricle is open along the margo acutus (Figure XIV-7 In opening the pulmonary valve the hea

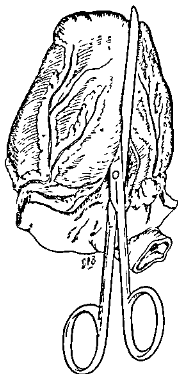


Figure XIV-7. Dissection of the isolated heart. The right ventricle is opened along the margo acutus

is placed so that the apex of the heart is directed towards the examiner. The enterotome in introduced into the right ventricle close to the apex along the line of incision that has just been made and the conus pulmonalis and the pulmonary valve are cut along the interventricular septum (Figure XIV-8). The incision should be extended into the main stem and left pulmonary artery

Next, the left atrium is inspected, and this is done after cutting through its wall, the line of cutting connecting the openings of the pulmonary veins. An excellent view is now obtained of the inside of the atrium including the mitral valve Next, the left atrium is incised along its left lateral wall, the incision extends through the mitral orifice and, continuing along its left lateral wall (margo obtusus), opens the left ventricle. During this incision the ventricle is held (Figure XIV-9) so that the apex is directed away from the examiner and the left lateral margin of the heart (margo obtusus) is directed toward him The next incision is designed to open the aortic valve. The left ventricle is again incised, the apex being directed towards the examiner, so that the line of incision extends from the apex (from the point reached by the incision that has just been made into the left ventricle) along the interventricular septum into the aorta, opening the aortic valve (Figure XIV-10) In doing so, that portion of the pulmonary trunk which remained attached to the heart is pulled ventrally to avoid cutting it.

Maresch and Chiari (1933) recommended the following technic which has been the routine procedure for many years at the Vienna Pathologic Institute. The heart is opened by means of four sections with the long knife (amputation knife). It is lifted from the pericardium and incised along its left lateral border. Both the left atrium and left ventricle are opened with the long knife, the *incision into the*

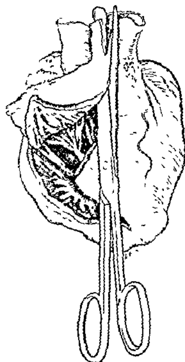


Figure XIV-8 Dissection of the isolated heart. The conus pulmonalis and pulmonary valve are cut along the interventricular septum

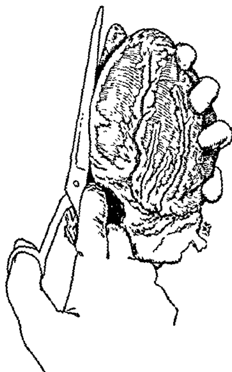


Figure XIV-9. Dissection of the isolated heart. Incision of left atrium and left ventricle. Note position of the heart,

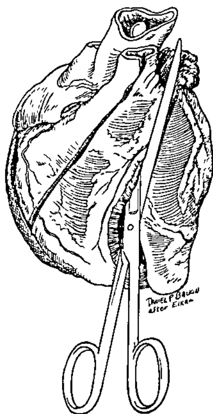


Figure XIV-10 Dissection of the isolated heart The aortic valve is opened by continuation of the incision shown in Figure XIV-9.

atrium being directed between the openings of the pulmonary veins. If the annulus fibrosis has not been opened by this incision, the mitral valve may now be opened either with the knife from within the ventricle or with an enterotome, the blade with the blunt end being introduced through the ventricle into the atrium The *second section* opens the right ventricle and right atrium with the knife and is similar to the one previously described, the heart being tilted upwards and the knife being introduced through the apex into the right ventricle and atrium, piercing from within the lateral atrial wall about halfway between the opening of the superior and inferior venae cavae. The tricuspid valve, if not diseased, is opened by this incision. The *next incision* opens the pulmonary valve and pulmonary trunk. This is done with the knife, cutting along the interventricular septum. The ventral wall of the right ventricle is held with the left hand, the four fingers being inside the ventricular cavity, while an assistant holds the ventral wall of the left ventricle extended, to facilitate the incision. The point of the knife is directed through the ventral wall of the pulmonary trunk and cuts through the ventral wall of the right ventricle close to and parallel to the septum. The entire right ventricle, pulmonary conus, pulmonary valve and a portion of the pulmonary trunk may now be viewed. The *fourth incision,* which is designed to complete the opening of the left ventricle and to expose the aortic valve, is the counterpart of the third. The left hand holds and extends the dorsal wall of the right ventricle close to the apex (an assistant holding and extending the ventral wall of the left ventricle) while the knife or enterotome is introduced into the left ventricle and cuts close to and along the septum from the apex upwards into the aorta, opening the aortic valve. Maresch and Chiari recommend turning the knife or the enterotome (Figure XIV-10) to the right immediately after opening the aortic valve so as to avoid injuring the pulmonic valve.

Gross Examination of Myocardium. After the heart has been dissected and the heart valves and the endocardium examined, the myocardium must be scrutinized. For the presence or absence of fatty infiltration of the myocardium it is best to examine the wall of the right ventricle and in particular that surface which has been exposed by cutting open the tricuspid valve. Early fatty infiltration is commonly found in this region of the myocardium. For vascular disturbances and possible gross evidence of inflammation it is best to make several cuts through the myocardium. First, the ventral flap of the left ventricle, between the lines of incisions made to open the aortic and mitral valves, is transected, the transection always extending parallel to the endocardial and

pericardial surfaces Thus the whole flap is transected. The second line of section cuts through the myocardium corresponding to the left lateral and dorsal wall of the left ventricle and through the interventricular septum. Both of these sections should be performed with the larger knife, the line of section covering as large an area as possible, best extending from the apical regions to about the level of the mitral valve. Again the incision is parallel to the endocardial and pericardial surfaces. Several longitudinal cuts may now be made through both atria and the right ventricle. It is also important to incise the interventricular septum by means of several *longitudinal cuts, after which the left and* right papillary muscles may be incised.

In disturbances of cardiac rhythm, and especially in instances of unexpected death, the areas of the myocardium in which the conduction system of the heart is located (see Figures III-24 to III-27) should be submitted to histologic examination The epicardial surface often presents a depression between the right atrium and the superior vena cava which corresponds to the location of the *sinus node*. The corresponding endatrial region usually contains a little more fat than the remainder of the atrium. This node does not produce a circumscribed elevated nodule and can be demonstrated only on histologic examination.

The atrioventricular node (Tawara) is located within the interatrial septum just cephalad to the junction of the right atrium and ventricle, and more specifically between the ventral margin of the coronary sinus (the opening of the cardiac vein) *and the region just cephalad to the attachment* of the medial leaflet of the tricuspid valve. This node also is not visible. Extending from the node is the bundle of His which runs through the annulus fibrosus to the interventricular septum just beneath the membranous septum where it divides into a right and left branch. Both branches are situated beneath the endocardium of the interventricular septum. They end as small branches in the subendocardial regions of the papillary muscles and columnae carneae. Occasionally one encounters small areas of thickening or calcification just beneath the membranous septum at points of subdivision of the bundle In extremely rare instances a minute tumor may be found at such a point (see page 892).

Selection of Sites for Cutting Blocks of Tissue. It is important to cut a number of blocks to include the valvular endocardium, the mural endocardium and the *myocardium of both ventricles and atria* for histologic examination. Often the entire explanation for a seemingly complicated case is found on histologic examination of the myocardium The blocks may be hardened in 10 per cent formalin* or in Zenker's formol.** Selection of sites for removal of blocks of myocardium is difficult. Those portions of the myocardium which grossly seem abnormal should always be examined histologically Routinely, sections should be taken from the interventricular septum, from the ventral wall of the left ventricle beneath the mitral valve, and from a corresponding portion of the dorsal wall of the left ventricle. Sections from the right ventricle should include a portion of the apical region on the ventral and dorsal walls and sections from both atria should include, when mural thrombi are present, portions of the thrombi with adjacent myocardium. Gross and associates (1930) recommended that

* "10 per cent formalin" is a 10 per cent aqueous solution of the commercial preparation of 38-40 per cent formaldehyde gas in water. Ten per cent formalin therefore represents a 4 per cent solution of formaldehyde in water (Formula: 40 per cent formaldehyde 10 ml, distilled water 90 ml)

** Zenker's formol (Helly's solution) consists of 90 ml of Zenker's solution and 10 ml. of 40 per cent formaldehyde. Zenker's solution consists of 2 5 Gm potassium dichromate, 5 0 Gm mercuric chloride, distilled water up to 100 0 ml.

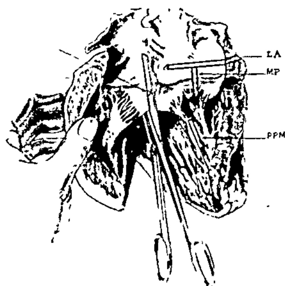


Figure XIV-11 Diagram of left atrium and ventricle (left inflow tract) showing the method of cutting the left atrium, mitral posterior, left posterior papillary muscle, and aorta, aortic valve and mitral valve blocks. (Taken from Gross, L., Antopol, W., and Sacks, B.. A standardized procedure suggested for microscopic studies on the heart With observations on rheumatic hearts, *Arch Path*, *10* 840-852, 1930 Reproduced by permission of the authors and the publishers.)

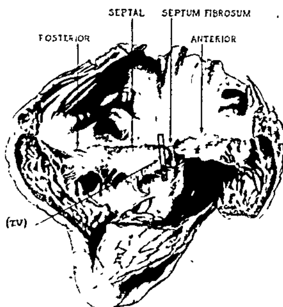


Figure XIV-12. Diagram of the right atrium and ventricle (right inflow tract), showing the method of cutting the tricuspid valve and septum (*T V.*) block (From Gross *et al.*)

blocks be cut from the following regions of the heart for histologic examination for Aschoff bodies: (1) *left atrium,* approximately 1 cm. above the insertion of the posterior leaflet of the mitral valve, to show the left atrial endocardium, subendocardium, myocardium and pericardium, and sometimes the coronary sinus; (2) *posterior mitral leaflet* with subjacent myocardium and endocardium, to show the left atrial endocardium and subendocardium, the myocardial wedge of the left atrium and the pericardial wedge of left ventricle, (3) *posterior papillary muscle,* to show myocardium, the endocardial covering and sometimes the insertion of the chordae tendineae; (4) area through the *aorta, aortic valve and anterior leaflet of the mitral valve* including the atrial endocardium, to show the left atrial endocardium, subendocardium, and myocardial wedge, the pericardial wedge, the root of the aorta, the aortic valve, and the sinus pocket (Figure XIV-11); (5) *pulmonary trunk and valve,* to show the pulmonary



Figure XIV-13. Low power magnification of mitral posterior (*M P.*) section. *A* indicates the left atrial endocardium; *B*, the left atrial subendocardium, *C*, the left atrial myocardial wedge; *D*, the pericardial wedge, *E*, the left ventricular myocardium; *F*, the ring of the posterior mitral valve, *G*, the posterior leaflet of the mitral valve, and *H*, the posterior mitral pocket. (From Gross *et al.*)

trunk and adjacent pericardium, the pericardium of the right ventricle, the pericardial wedge, the pulmonary valve, the subpulmonic angle, the pulmonary ring and the right ventricular myocardium, and (6) *tricuspid valve*, the entire thickness of the septum and adjacent atrium, to show the right atrial endocardium, subendocardium and myocardium, neuromuscular bundle, septum fibrosum, tricuspid ring, tricuspid valve, interventricular septum and the tricuspid pocket, and sometimes a portion of the aortic valve (Figures XIV-11 to XIV-16).



Figure XIV-14 Low power magnification of the aorta, aortic valve and mitral valve (*A M V.*) section *A* indicates the left atrial endocardium, *B*, the left subendocardium, *C*, the left atrial myocardial wedge; *D*, the pericardial wedge, *E*, the root of the aorta, *F*, the aortic valve, *G*, the sinus pocket, *H*, the aortic ring, *I*, the subaortic angle, *K*, the mitral-aortic intervalvular fibrosa and endocardium, *L*, the mitral ring, and *M*, the anterior or aortic flap of the mitral valve. (From Gross *et al.*)

These six blocks include all four valves and valvular rings, the pericardium of the right and left sides of the heart, the left and right atria, the myocardium of the right and left ventricles, interventricular septum and left posterior papillary muscle, the bases of the aorta and pulmonary trunk, the pericardial wedge abutting against the valve rings, the neuromuscular bundle and the coronary sinus.

Note on Opening Hearts with Congenital Malformations. It is impossible to give one universally acceptable method of opening all hearts with congenital malformations. It cannot be too strongly emphasized that a heart with a congenital defect should be opened only by the experienced pathologist who, after orientation, can visualize the type of anomaly that is likely to be present in the particular instance Only the experienced examiner can deviate from a given routine, can devise a special technic and still demonstrate all the malformations present. It is important for one not only to convince himself of the pertinent anomalies, but also to be able to demonstrate them, to retain the specimen, to photograph it and to use it for further studies. If, however, the heart is mutilated, even the prosector may be unable to demonstrate the principal anomaly. In the following description, an outline of procedures for a few given types is presented. The prosector must always be cautious in cutting, should use the probe more often than the scissors, and should inspect carefully and use blunt dissection often to clarify a complex anomaly rather than observe a too-strict adherence to the routine

If congenital cardiac anomalies are an-



Figure XIV-15 Low power magnification of the pulmonary artery and valve (P A V) section. *A* indicates the pulmonary artery and investing pericardium, *B*, the pericardium of the right ventricle, *C* the pericardial wedge, *D*, the pulmonary valve, *E*, the subpulmonic angle, *F*, the pulmonary ring, and *G*, the right ventricular myocardium (From Gross *et al.*)

ticipated, it is essential to remove the heart and all adjacent structures *en masse*. The ascending aorta and a portion of the descending thoracic aorta should be left in continuity with the heart, also the lungs with the pulmonary arteries and veins, the superior vena cava and its main tributaries and the small portion of the inferior vena cava between the diaphragm and right atrium

In general, the dissection of the heart starts with the opening of the veins and right atrium and follows the direction of the flow of blood. The mouths of the venae cavae are usually not opened. Edwards (1949) recommends a transverse incision in the *central* wall of the right atrium. Thus, the interatrial septum can be fully examined and also the region of the tricuspid valve. If the latter is atretic no attempt should be made to force it open. The medial leaflet of the tricuspid valve should be especially carefully scrutinized since it may partially cover an open membranous interventricular septum. Before the right ventricle is opened the pulmonary trunk and aorta should be examined in regard to their size, relative positions and region of origin from the ventricles. If at first only one vessel is found emerging



Figure XIV-16. Low power magnification of the tricuspid valve and septum (T V) section. *A* indicates the right atrial endocardium, *B*, the right atrial subendocardium, *D*, the neuromuscular bundle, *E*, the septum fibrosum, *F*, the tricuspid ring, *G*, the tricuspid valve, *H*, the interventricular septum, and *J*, the tricuspid pocket (From Gross *et al*)

from the ventricle a search must be made for another, perhaps a small vessel, an atretic vessel or a cordlike structure close by. Before the pulmonary valve is opened, it should be probed from within the right ventricle, special care being taken that the probe actually extends into the pulmonary trunk and not into the aorta through a patent ventricular septum. The size of the conus pulmonalis should be determined. The conus may be so large as to simulate a third ventricle. After the pulmonary trunk is opened, one glance at the sinuses of Valsalva should confirm the absence of the mouths of the coronary arteries. It sometimes happens that the scissors introduced into the pulmonary trunk will enter a patent ductus arteriosus. It must be remembered that sometimes the open ductus is equal in size to each of the pulmonary arteries and appears as a direct continuation of the pulmonary trunk. If the pulmonary trunk is narrowed or atretic it should not be slit open. Its course should first be followed and if its two branches, which are caudad to the origin of the ductus arteriosus, are of normal size or dilated, these may be opened and through their lumina one may inspect the pulmonary trunk.

The left atrium should be opened with scissors, starting the dissection by cutting through the wall of one of the pulmonary veins and, after the incision has reached the atrial lumen, by extending the line of incision from the opening of one pulmonary vein to the others. Next, the region of the interatrial septum and the atrial sur-

face of the mitral valve should be scrutinized. The left ventricle is opened along its left lateral margin (margo obtusus) and the ventricle examined immediately. It should always be ascertained at this point, if it has not been done previously, if there is a patency of the septum. A probe should be introduced into the aorta and the aortic valve examined. Sometimes the probe which is thought to be in the aorta has extended through a patency of the septum into the pulmonary trunk or a transposed aorta. It must now be determined, before another incision is made, if there is a riding aorta carrying blood from both ventricles or a transposition of greater degree. In such instances it is best to avoid a second incision into the left ventricle. The ventricle may be viewed through the previous incision and the aortic valve through an opening in the wall of the aorta; or an incision may be made along the ventricular septum up to the region of the membranous septum and the root of the aorta viewed from there.

In instances of stenosis of the isthmus the collaterals should be demonstrated. It is also wise to seek routinely the bronchial arteries. In cases with pulmonary stenosis this is imperative. If facilities are available the bronchial arteries may be injected with a plastic material and the lungs subsequently macerated (see Hales and Liebow, 1948). According to Edwards (1949), the bronchial arteries are always removed along with the thoracic organs. When these arteries are dilated they are easily identified as tortuous wide vessels arising either directly from the aorta, the intercostal arteries, or from the major branches of the aortic arch. It is also recommended that one inspect the relationship of the aorta to the trachea, bronchi and esophagus. The origin, course, and distribution of the coronary arteries must be examined in every instance. Abnormalities in their course may indicate transposition of the arterial trunks.

Examination of Coronary Arteries

Dissection and Distribution. The left coronary artery is opened from its mouth. The scissors are used to cut the short main coronary artery, then the anterior descending and circumflex branches and the two main branches of the latter, the ramus anterior ventriculi sinistri and the ramus marginis obtusi. The right coronary artery is opened from the point at which it was cut when the right ventricle was first incised. The artery is easily located within the coronary sulcus. First, the portion of this artery proximal to the site of previous section is opened, to a point just short of its mouth; cutting through its mouth should be avoided to protect the wall of the sinus of Valsalva. Next, the distal portion of this artery is opened, and along with it the posterior descending branch. A number of closely spaced cross-sections of the main coronary arteries and their principal branches should be made, particularly when the coronary arteries are severely sclerosed and their lumens markedly narrowed. The advantage of this method lies in the fact that very recent thrombi are not displaced. Figure XIV-17 shows the distribution of the branches of the coronary arteries which should be opened. It is adapted from Spalteholz (1924) and uses his nomenclature. Figure XIV-18 shows the distribution of the coronary arteries which, according to Spalteholz, occurs in from 5 to 17 per cent of hearts. Here the right coronary is the predominating artery, its terminal branch being the ramus marginis obtusi instead of the posterior descending. In about 10 per cent of cases the left coronary artery is the predominating artery, its final branch being the posterior descending artery (Figure XIV-19). Particular care must be taken

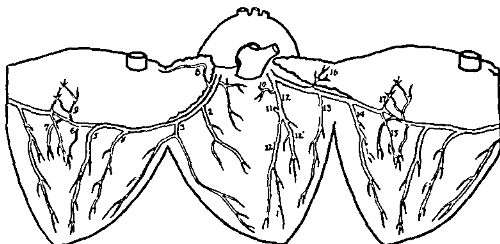


Figure XIV-17 The distribution of the coronary arteries as found in 80 per cent of adult human hearts (over 30 years of age). (Adapted from Spalteholz.)

BRANCHES OF THE RIGHT CORONARY ARTERY

1 Arteria adiposa dextra
2 Ramus ventriculi dextri anterior
3 Ramus marginis acuti
4 Ramus ventriculi dextri posterior
5 Ramus sulci longitudinalis posterioris
6 Ramus ventriculi sinistri posterior
7 Ramus ventriculi sinistri posterior accessorius
8. Ramus atrialis dexter anterior
9 Ramus atrialis sinister posterior

BRANCHES OF THE LEFT CORONARY ARTERY

10 Arteria adiposa sinistra
11. Arteria septi ventriculorum
12 Ramus collateralis descendens anterior
12′ Ramus primus 12″ ramus secundus
13 Ramus ventriculi sinistri anterior
14 Ramus marginis obtusi
15 Ramus ventriculi sinistri posterior
16 Ramus atrialis sinister anterior
17 Ramus atrialis sinister posterior

in all instances to dissect and open carefully all main branches of the coronary arteries. It is essential not to discontinue the dissection of the coronary arteries after one occluding lesion has been found but, routinely, to examine all of the main coronary arteries

INJECTION OF THE CORONARY ARTERIES

In addition to the anatomic dissection of the coronary arteries, their distribution and patency have been studied by use of injection mediums. As early as 1885 Hyrtl injected the coronary vessels with a metallic alloy of low-melting point. Subsequent corrosion of the heart muscle revealed the pattern of the coronary distribution. Van der Ghinst (1949) applied a similar technic using a plastic material (Plexene). This method also sacrifices the heart muscle, and alterations in the vessels cannot be correlated with myocardial lesions. One may visualize the distribution of the coro-

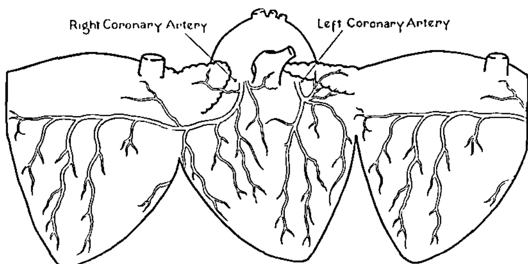


Figure XIV-18 The distribution of the coronary arteries as found in 5-17 per cent of adult human hearts (Adapted from Spalteholz) The right coronary artery here predominates, the ramus marginis obtusi being the terminal branch of the left coronary artery.

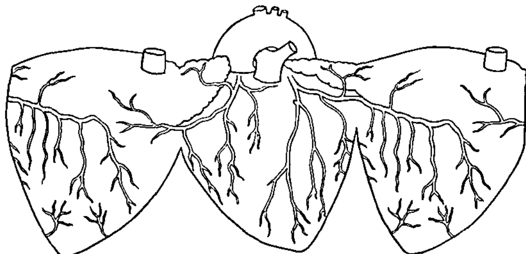


Figure XIV-19 The distribution of the coronary arteries as found in about 10 per cent of adult human hearts (Adapted from Spalteholz) The left coronary artery predominates, its final branch being the ramus ventriculi sinistri posterior (posterior descending artery)

naries and locate alterations in them by injection of the arteries with radiopaque material and subsequent roentgenography of the heart Gross (1921) devised a technic for injecting the coronary arteries with barium sulfate suspension in gelatin under pressure, by employing a standardizing and calibrating device. This technic or modifications and extensions of it have been widely employed with varying results and for specific purposes. In order to obtain an estimate of the capacity of the coronary arteries during life in hypertensive and ischemic hearts, Harrison and Wood (1949) injected the arteries with radiopaque gelatin at the known diastolic pressure of the patient. Because their skiagrams did not distinguish whether points of narrowing represented sites of atheroma or of canalized thrombi and because it was repeatedly noted that at sites of actual narrowing the skiagram might reveal no abnormality, they carefully checked their radiographic findings anatomically and histologically (Figure XIV-20).

Because the method of Gross did not

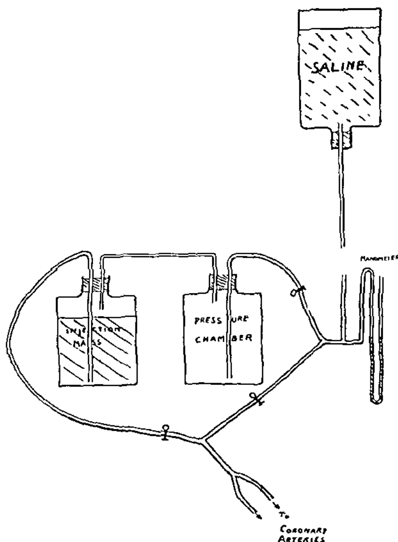


Figure XIV-20 Diagram of Harrison and Wood's apparatus for injection of coronary arteries with radiopaque gelatin (From Harrison, C V, and Wood, P Hypertensive and ischaemic heart disease, a comparative clinical and pathological study, *Brit Heart J*, *11* 205-229, 1949 Reproduced by permission of authors and publisher.)

reveal the distributions of minute or penetrating branches of the coronary vessels, Schlesinger and associates (1938), after injection (of lead phosphate in agar), sectioned the heart in a manner designed to expose the remote ramifications of the coronary tree for radiography. Sections were so disposed that the conical heart muscle was unrolled to make all the vessels lie in the same flat plane This made all vessels, regardless of their normal relationships, equally visible roentgenologically and was particularly valuable in demonstrating alterations in otherwise obscure twigs to the septum.

To insure penetration of small branches of the coronaries, Prinzmetal and associates (1942) altered the injection medium, using an injection medium with a viscosity approaching that of blood. They determined the quantitative collateral circulation by clamping the coronary vessels alternately and measuring volumes of material injected.

To determine collateral circulation, various dyes have been employed in the injection medium with some success and with varied results Several technics for injection are briefly described below.

Gross (1921) originally injected the coronary arteries 48 hours postmortem, after rigor had subsided. However, this interval may be varied considerably, the injections performed within a few hours postmortem or after the hearts have been at ice-box temperature for several days. To overcome rigor, the heart is placed in saline at 37 C for four hours. The injection is performed with the heart and all injection material at standard temperature.

Technic of Gross for Injection of Coronary Arteries. Cardiac chambers are washed free of blood clot. The loose tissue about the aorta is bluntly dissected free to expose the coronary arteries at their sites of emergence. A cannula is inserted into each coronary orifice, each cannula being a snugly fitting flanged-glass nozzle. A silk thread is looped about the coronary artery close to its point of emergence from the aorta, the flanges of the cannula being below the loop which is tightened about the cannula. Rubber tubing is attached to the cannulae and connected by a Y-tube. The heart is suspended by inserting a glass rod under the bridge of the pericardium which lies between the great vessels and the atria, and this rod is supported on a tripod.

To maintain standardized mechanical factors, Gross devised a double-decked or duplex incubating apparatus. The cannulated heart is suspended in the upper chamber on a tripod. The lower chamber contains the injection mass and saline solution, each in a sealed or capped container, maintained at standard temperatures by electric immersion heaters. A compressed air tank with pressure gauge or mercury manometer and outlet tube can be connected by conduits to inlets in either the saline or the injection mass, the contents of the container being forced through an outlet tube. Both outlet tubes extend to the upper chamber of the apparatus where they can alternately be attached to the coronary cannulae. The coronary arteries are washed clean with saline. Then the pressure tube is connected with the flask containing the injection mass. The mass is forced into the vessels until the mercury manometer reading remains constant at 150 mm. without additional pressure. The vessels are tied off, cannulae removed and the heart immersed in cold water. With a suction apparatus the chambers of the heart are freed of any accumulated injection mass. The heart is then immersed in cold formalin until it is fixed and bleached, when it is ready for preparation of the stereoscopic roentgenogram.

To avoid objections that the stereoscopic roentgenogram of the heart does not give a clear precise picture of the specific vessel involved, or does not visualize the smaller twigs of the coronaries, Gross and Kugel (1933-34) modified this original technic by slicing the injected and fixed heart transversely into strips of equal thickness (7 mm.) and took roentgenograms of them so that direct comparison could be made of the vasculature within the wall of the right and left ventricles and the interventricular septum. Transverse sections were made from the atrioventricular sulcus one-third of the way down to the apex.

Schlesinger's Method. The heart is warmed in a bath of physiologic saline at 44° C. A thermometer is placed directly into the chamber of the left ventricle, which is the slowest to reach the desired temperature. The entire procedure is conducted in a saline bath kept at 44-45° C. Schlesinger cannulates the arteries and connects them individually by tubes to receptacles containing injection mass or saline. Each receptacle is connected to a

separate manometer and by means of a Y-tube, both to the same syringe which supplies pressure. Three-way stopcocks permit pressure (of the syringe) to force the injection mass through both coronaries simultaneously or through right and left alternately. Injections are continued until manometer readings remain constant at 150 mm. of mercury for five minutes. To insure flow through anastomotic channels, the pressure to the left coronary is reduced to 0 or lower, and that to the right artery is kept at 150 mm. for several minutes. The process is then reversed with pressure to the right coronary reduced and that to the left maintained at 150 mm. The cannulae are clamped with the pressure at 150 mm and the heart is disconnected The mass is set by cooling the heart in a bath of iced physiologic salt solution. The injection medium is colored with methyl blue and basic fuchsin (in saturated alcoholic solution) for the right coronary artery and the left coronary artery, respectively.

After injection of the heart, the injection mass is allowed to harden and then the heart is incised according to a prescribed technic in order to unfold the heart and permit small vessels, regardless of their situation *in vivo*, to be visualized roentgenographically.

Prinzmetal's Method. Prinzmetal and coworkers (1942) attempted to demonstrate the distribution of the coronary system by the injection of a "more physiologic" medium, having a viscosity similar to that of blood and consisting of a mixture of lead carbonate, mercuric sulfide and gelatin with a viscosity of 5.40 as compared with 4.07 for blood. Prinzmetal and associates (1947) used radioactive erythrocytes which were found to penetrate the smallest branches of the coronary system. Human red cells were made radioactive by incubation with radioactive phosphorus in the form of Na_2HPO_4. The radioactive erythrocytes in saline solution were perfused at a constant pressure of 100 mm. Hg, until the perfusate was seen to issue from the coronary sinus. The total amount of fluid perfused through the heart in each experiment was from 30 to 60 ml. and the time required was 30 to 60 seconds. The heart was then unrolled according to the method of Schlesinger The distribution of the radioactive erythrocytes was determined by a Geiger counter at arbitrarily chosen sites on the endocardial and pericardial surfaces of the heart. By exposing the heart to x-ray films for from 15 to 48 hours, a radioautograph was obtained.

In another method, Prinzmetal injected into one coronary artery glass spheres of diameters ranging from 10 to 400 micra These were suspended in a radiopaque mixture Glass spheres injected into one coronary artery were recovered from the opposite coronary, the ventricular cavities and the coronary sinus. The diameters of the various anastomotic channels were thus determined by the size of the spheres recovered. Salans and Tweed (1947) described a rapid technic using Neoprene, a synthetic latex. Each coronary was washed separately with saline. Barium sulfate in aqueous ammoniated solution of latex rubber was employed because it provides maximum radiopacity and because with it one may consistently obtain injection of precapillary arterioles that have a diameter of 15 to 75 micra. The medium is prepared with red and blue organic dyes for left and right coronaries, respectively. During injection, the heart is suspended for five to 15 minutes in a solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde in 70 per cent ethyl alcohol. The heart is then fixed *in vacuo* at low temperature for 20 minutes, after which time it is cut according to the method of Schlesinger. This technic eliminates the use of

an unstable injection medium, such as lead phosphate agar of Schlesinger which does not penetrate the small vessels consistently, and the prolonged exposure to a temperature of 44° C. It permits preparation of corrosive specimens as well as specimens suitable for dissection.

WEIGHT AND MEASUREMENTS OF THE HEART

In measuring the heart one must take into consideration the size of the chambers and the presence or absence of rigor mortis The technic of opening the heart must not vary Measurements of the thickness of the walls of the right and left ventricles must always be taken in similar locations and care must be taken not to include the thickness of the trabeculae and papillary muscles

The old rule that normally the size of the heart corresponds to that of the closed fist of the patient is inaccurate and should be discarded The weight of the normal heart in an adult is usually stated to be between 275 and 325 grams Nauwerck (1921) gave the weight of the heart of the male as 300 grams and of the female as 250 grams Smith (1928) concluded that the average weight of the adult male heart s 295 grams, and the average weight of he adult female heart 250 grams. His study excluded those hearts in which the records disclosed conditions known or believed to affect the weight of the heart. Thus, his figures were obtained by rigid selection of 1000 hearts from 6000 that were available for the study. He concluded that there is a definite correlation between the weight of the heart and the weight of the body and established the ratio as 0.43 per cent for males, and 0.40 per cent for females. The ratio is slightly higher in thin persons and lower in obese persons. This coefficient is less accurate for body weights of less than 45 Kg. (100 pounds) and more than 91.5 Kg. (210 pounds). Table XIV-1 lists weights of normal hearts, according to Smith.

Zeek (1942) reported a statistical analysis of the weights of hearts from 926 adult bodies in which no clinical or pathologic evidence of heart disease or of any commonly recognized cause of myocardial hypertrophy was found. Her study revealed the following factors to have an effect on the weight of the heart: body weight, sex, body length and state of body nourishment No effect of age or race on heart weight was demonstrated. Table XIV-2 is taken from her study.

Roessle and Roulet (1932) gave tables of weights of the hearts in males and females (Tables XIV-3 and XIV-4) and

TABLE XIV-1

Normal Weights of Heart of Human Males and Females in Relation to Body Weight (Smith, 1928)

Body Weight				*Weight of Heart*					
Pounds		*Kilograms*		*Minimum, Grams*		*Average, Grams*		*Maximum, Grams*	
M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
105	90	47	40	165	135	205	162	241	193
110	95	50	43	173	143	215	171	253	204
115	100	52	45	181	150	225	180	264	215
120	105	54	47	190	158	235	189	276	226
125	110	56	50	198	165	245	198	287	237
130	115	58	52	206	172	255	207	299	248
135	120	60	54	213	180	265	215	310	259
140	125	63	56	221	188	274	225	322	268
145	130	65	58	229	195	284	234	333	277
150	135	68	60	237	203	294	244	345	286
155	140	70	63	245	211	304	253	356	295
160	145	72	65	253	219	313	262	368	304
165	150	74	68	261	225	323	272	370	313
170	155	77	70	268	233	333	282	371	322
175	160	79	72	280	240	343	288	372	330
180	165	81	74	288	247	353	297	373	337
185	170	83	77	296	255	363	306	382	343
190	175	86	79	304	283	373	315	392	350
195	180	88	81	312	301	382	324	402	356
200	185	90	83	320	309	392	333	412	361
	190		86		317		342		366
	195		88		325		351		371

weights of various parts of the heart (Table XIV-5)

Coppoletta and Wolbach (1933) gave the weights of hearts of infants and children (Table XIV-6).

TABLE XIV-2

[illegible]

Body Length, Cm	Heart Weight, Gm		Body Length, Cm	Heart Weight, Gm.	
	Males $\sigma = \pm 40$	Females $\sigma = \pm 30$		Males $\sigma = \pm 40$	Females $\sigma = \pm 30$
135	254	219	168	317	277
136	256	220	169	319	279
137	258	222	170	321	281
138	260	224	171	323	283
139	262	226	172	325	284
140	264	227	173	327	286
141	266	229	174	329	288
142	268	231	175	330	290
143	270	233	176	332	291
144	272	235	177	334	293
145	273	236	178	336	295
146	275	238	179	338	297
147	277	240	180	340	299
148	279	242	181	342	300
149	281	243	182	344	302
150	283	245	183	346	304
151	285	247	184	348	306
152	287	249	185	349	307
153	289	251	186	351	309
154	291	252	187	353	311
155	292	254	188	355	313
156	294	256	189	357	315
157	296	258	190	359	316
158	298	259	191	361	318
159	300	261	192	363	320
160	302	263	193	365	322
161	304	265	194	367	323
162	306	267	195	368	325
163	308	268	196	370	327
164	310	270	197	372	329
165	311	272	198	374	331
166	313	274	199	376	332
167	315	275	200	378	334

σ = standard deviation

TABLE XIV-3

Weight of Heart in Males
(Roessle and Roulet, 1932)

Age	*Mean Heart Weight in Grams*	*Mean Body Weight in Kilograms*	*Number of Cases*
Birth	23 37	3 373	60
Birth–6 months	28 20	3 430	15
7–12 months	38 8	4 47	5
1 year	58 93	12 360	6
2 years	64 125	12 147	4
3 years	74 58	15 300	6
4 years	83 71	18 433	7
5 years	98 00	17 375	3
6 years	104 00	—	1
7 years	119 00	20 400	4
8 years	113 5	—	2
9 years	116 00	20 800	1
10 years	185 00	31 000	1
11 years	140 00	27 000	1
12 years	160 1	37 600	4
13 years	198 00	37 850	2
14 years	—	—	—
15 years	241 75	44 900	8
16 years	252 70	43 812	7
17 years	279 00	49 340	7
18 years	217 25	42 400	4
19 years	285 00	55 990	20
20 years	282 07	51 998	13
21–25 years	305 48	55 125	90
26–30 years	312 02	51 617	69
31–35 years	314 29	55 714	74
36–40 years	312 19	54 635	61
41–45 years	317 23	57 255	51
46–50 years	335 64	56 400	28
51–55 years	346 81	58 800	16
56–60 years	333 57	54 066	21
61–65 years	324 42	53 380	14
66–70 years	359 33	59 400	9
71–75 years	308 33	45 430	6
76–80 years	318 00	47 400	2
85–90 years	321 00	43 450	2

TABLE XIV-4

Weight of Heart in Females
(Roessle and Roulet, 1932)

Age	*Mean Heart Weight in Grams*	*Mean Body Weight in Kilograms*	*Number of Cases*
Birth	21 4	3 198	44
Birth–6 months	21 37	3 396	8
7–12 months	36 33	5 18	3
1 year	53 66	9 262	6
2 years	54 21	11 166	7
3 years	65 8	12 450	5
4 years	71 75	—	4
5 years	90 8	18 000	5
6 years	82 16	—	3
7 years	94 5	—	2
8 years	109 00	19 200	2
9 years	115 00	23 800	3
10 years	118 00	26 000	1
11 years	135 00	29 500	1
12 years	166 00	—	2
13 years	170 00	—	2
14 years	201 00	42 2	2
15 years	201 33	36 700	3
16 years	204 5	50 225	4
17 years	220 00	47 660	3
18 years	225 5	44 550	4
19 years	254 6	47 830	3
20 years	262 25	56 100	8
21–25 years	265 8	50 441	14
26–30 years	252 6	51 705	21
31–35 years	269 5	55 270	4
36–40 years	233 14	49 010	7
41–45 years	288 36	55 300	11
46–50 years	298 88	56 344	9
51–55 years	292 4	60 540	13
56–60 years	316 33	56 940	12
61–65 years	307 68	50 240	16
66–70 years	362 00	53 625	4
71–75 years	309 5	48 000	7
76–80 years	335 4	48 340	5
81–85 years	292 33	37 400	6
86–90 years	284 00	34 1	2
Over 90 years	239 00	28 950	2

TABLE XIV-5

Weight of Various Parts of the Heart
(Roessle and Roulet, 1932)

Age	*No. of Cases*	*Body Weight in Kilograms*	*Weight in Grams*							
			Gross Heart	*Left Ventricle*	*Right Ventricle*	*Inter-ventricular Septum*	*Left Atrium*	*Right Atrium*	*Interatrial Septum*
MALES										
6-10 years	2	22 5	123 00	38 5	22 5	22 75	—	—	—
11-14 years	3	32 26	166 6	54 3	27 8	37 6	8 5	10 00	11 00
15-20 years	14	53 73	264 3	83 2	45 5	60 2	19 00	13 00	13 00
21-30 years	24	56 35	303 3	91 8	50 8	68 3	—	—	—
31-40 years	23	54 7	297 2	85 5	49 7	63 6	17 00	12 5	9 5
41-50 years	6	53 82	317 8	86 75	48 5	64 6	17 5	23 00	18 00
FEMALES										
1- 5 years	1	14 00	50 00	18 00	10 00	11 00	—	—	—
15-20 years	4	51 25	255 5	79 75	41 12	55 75	11 00	12 5	12 5
21-30 years	2	58 00	227 00	68 5	41 5	47 00	17 00	13 00	9 00
31-40 years	2	49 5	328 00	84 00	48 00	61 5	—	—	—
41-50 years	1	55 00	376 00	105 00	52 00	68 00	—	—	—

TABLE XIV-6

Weights of Hearts of Infants and Children
(Coppoletta and Wolbach, 1933)

Age	*Body Length Cm*	*Heart Weight Gm.*
Birth to 3 days	49	17
3 to 7 days	49	18
1 to 3 weeks	52	19
3 to 5 weeks	52	20
5 to 7 weeks	53	21
7 to 9 weeks	55	23
9 to 3 months	56	23
4 months	59	27
5 months	61	29
6 months	62	31
7 months	65	34
8 months	65	37
9 months	67	37
10 months	69	39
11 months	70	40
12 months	73	44
14 months	74	45
16 months	77	48
18 months	78	52
20 months	79	56
22 months	82	56
24 months	84	56
3 years	88	59
4 years	99	73
5 years	106	85
6 years	109	94
7 years	113	100
8 years	119	110
9 years	125	115
10 years	130	116
11 years	135	122
12 years	139	124

Valve Measurements. The figures that are usually given as the average of the normal valvular orifices of the adult heart, namely, aortic 7-8 cm., mitral 9-11 cm., pulmonic 8-8.5 cm., tricuspid 11-13 cm., are approximately correct. It is stated that measuring orifices by insertion of fingers or of a graduated wooden cone does not take into account the tonus or elasticity of the muscle (see Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 1939).

Kopsch (1914), quoting Bizot, Wulff, Peacock, and Bouillaud, gave the circumferences of the various valves as shown in Table XIV-7.

TABLE XIV-7
Circumference of Valves, in Millimeters
(Kopsch, 1914)

Valve	*Bizot*		*Wulff*		*Peacock*		*Bouillaud*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Max.*	*Min.*
Tricuspid	123 6	107 5	129 7	124 5	115 3	101 6	108 4	106 1
Mitral	110 4	92 7	117 2	113 8	97 4	91 0	104 5	88 0
Pulmonic	71 8	66 9	——	——	84 7	82 5	76 7	67.7
Aortic	70 4	64 1	——	——	76 2	72 0	72 2	63 2

Kaufmann (1922) gave the measurements of the orifice of the mitral valve as 10 cm., of the aortic orifice as 7 cm., of the pulmonic as 8 cm. and of the tricuspid as 12 cm. Hurwitt (1947) studied the size of the pulmonic valve of children. His results are given in Table XIV-8.

TABLE XIV-8

Size of Pulmonary Trunk and Valve in Children According to Age (Hurwitt, 1947)

Age	No of Cases	*Body Length (Cm)*			*Weight of Heart (Gm.)*			*Circumference of Pulmonary Trunk (Mm)*			*Average Diameter of Pulmonary Valve (Mm)*
		Smallest	*Largest*	*Average*	*Smallest*	*Largest*	*Average*	*Smallest*	*Largest*	*Average S.D.**	
Prematures	251	28	48.5	43	3	36	13	10	30	19.5 ± 5.4	6.3 ± 1.8
N B.-3 mos.	222	49	64	52	6	50	19	15	42	24.7 ± 3.1	7.9 ± 1.0
3-6 mos.	97	50	68	59	12	94	29	18	48	28.7 ± 3.7	9.2 ± 1.2
6-9 mos.	67	51	113	65	20	74	36	20	48	31.2 ± 4.9	10.1 ± 1.6
9-12 mos.	44	50	78	68	25	72	42	21	58	32.9 ± 6.1	10.6 ± 1.9
12-18 mos.	67	64	87	75	28	84	49	21	59	34.9 ± 4.1	11.2 ± 1.3
18-24 mos.	34	58	91	81	36	105	61	25	52	36.4 ± 4.5	11.7 ± 1.5
2-3 yrs.	51	70	103	88	35	176	66	32	65	41.2 ± 6.6	13.3 ± 2.1
3-4 yrs.	30	66	113	93	50	130	77	33	65	41.3 ± 5.9	13.3 ± 1.9
4-5 yrs.	24	93	118	105	19	185	91	35	58	43.1 ± 5.7	13.9 ± 1.8
5-6 yrs	33	83	126	107	48	178	99	30	80	44.8 ± 6.1	14.4 ± 1.9
6-7 yrs.	12	112	131	119	86	202	112	35	50	44.2	14.3
7-8 yrs.	14	109	134	128	75	156	113	44	70	50.0	16.1
8-9 yrs	13	110	138	127	100	206	155	40	60	52.5	16.9
9-10 yrs.	13	97	151	130	82	280	150	40	70	51.5	16.7
10-11 yrs.	9	122	143	127	116	345	174	40	62	53.6	16.9
11-12 yrs.	10	103	145	138	105	356	191	40	70	54.1	17.5
12-13 yrs	5	143	162	151	178	286	224	45	69	56.0	18.1
13-14 yrs	1			168			597			70.0	21.9
14-15 yrs	1			165			272			62.0	20.0
15-16 yrs	2	120	160	140			240	45	70	57.5	18.6

* These figures represent the standard deviation of the distribution Approximately 68 per cent of the cases will fall within a range included by the average ± once the standard deviation, and 95 per cent within a range included by the average ± twice the standard deviation The number of cases in the age groups above six years is too small for this type of analysis

Kaufmann stated that in measuring the thickness of the heart it is important to state the exact site that is measured The pericardial fat tissue and the trabecular muscles should not be included in the measurements. He gave the thickness of the right ventricle as 0.5 to 0.7 cm., that of the left ventricle as 1.1 to 1.4 cm. His measurements of the wall of the right ventricle are obviously too large, its average thickness probably being only 2 to 3 mm.

For practical purposes it may be well to list the measurements given by Saphir (1951). They are only averages but will suffice in most instances (Table XIV-9)

TABLE XIV-9

Thickness of Walls of Heart and Circumference of Valves (Saphir, 1946)

*Thickness * of Wall of Chambers, Mm*	
Right and left atria	1-2
Left ventricle	8-10
Right ventricle	2-3
Circumference of Valves, Cm	
Mitral	10
Aortic	7.5
Pulmonic	8.5
Tricuspid	12

* Note In measuring the thickness of the ventricles, care must be taken not to include the thickness of the papillary muscles and columnae carneae

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This Book

PATHOLOGY
of the HEART

Edited by S E. GOULD, M.D., D.SC.

was set, printed, and bound by the Pantagraph Printing and Stationery Company, of Bloomington, Illinois. The engravings were made by the Capitol Engraving Company, of Springfield, Illinois The page trim size is 6⅛ x 9¼ inches The type page is 35 x 53 picas The type face is Caledonia, set 11 point on 13 point The text paper is Warren's White Lustro Gloss The cover is DuPont Fabrikoid, Quality 750, Color 5025, Grain, Shoe-4; Pliability, Medium, Finish, Cordoba P-1096



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